

A13  
cont.

56. The method as defined in Claim 55 where in the compound employed  $(CH_2)_m$  is  $CH_2$ .

# REMARKS

Claims 2 to 5, 10, 14, 16 to 18, 20 to 22, 26 to 28, 31, 34, 37, 39, 40, 50, 55 and 56 are present.

The invention in this application involves method of use claims 34, 36 and pharmaceutical combination Claim 37 and claims dependents thereon. These claims have been divided out of parent application Serial No. 09/812,960, now allowed.

The addition of  $R^3$  as polyhaloalkylaryloxycarbonyl in Claim 1 is based on original Claim 10, lines 29-30.

Claims 34 to 37 have been combined.

Claims 39, 42, 44 and 47 have been combined.

Claims 40, 43, 45, 48 and 49 have been combined.

Claims 50 and 51 have been combined.

The compounds claimed in the method of use and pharmaceutical combination claims are those which have been allowed in parent application Serial No. 09/812,960. Accordingly, it is submitted that the methods of use and combinations claimed herein which include the compounds allowed in parent application Serial No. 09/812,960 are patentable as well.

Accordingly., it is submitted that Claims 2 to 5, 10, 14, 16 to 18, 20 to 22, 26 to 28, 31, 32, 34, and 36 to 56 are patentable for the same reasons that the compounds of parent application Serial No. 09/812, 960 have been deemed patentable. Thus, it is believed that the above claims are in condition for allowance.

Respectfully submitted,



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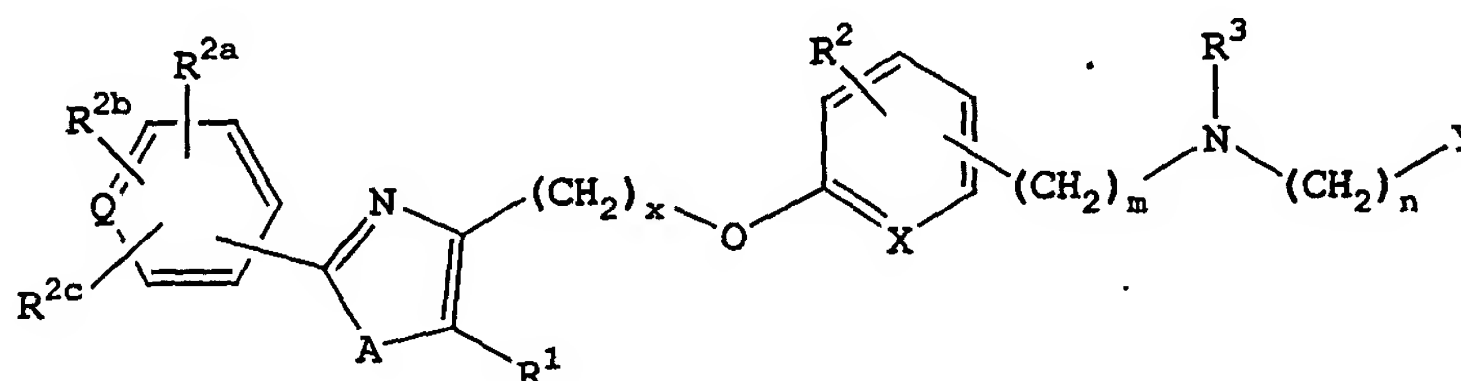
Date: 2/22/02

VERSION WITH MARKINGS TO SHOW CHANGES MADE

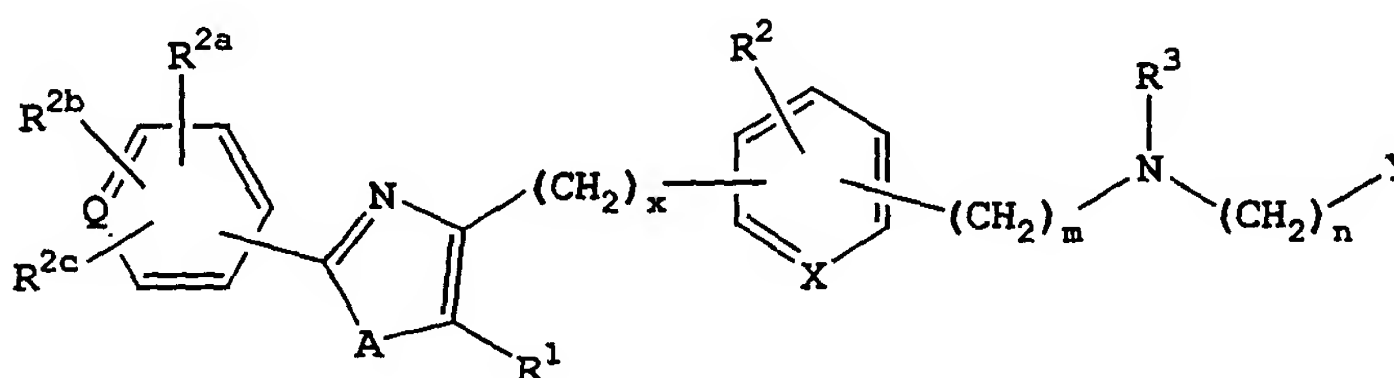
Please cancel Claims 1, 6 to 9, 11 to 13, 15, 19, 23 to 25, 29, 33 and 35.

Please amend Claims 2 to 5, 10, 14, 16 to 18, 20 to 22, 26 to 28, 30 to 32, 34, 36 and 37 as follows.

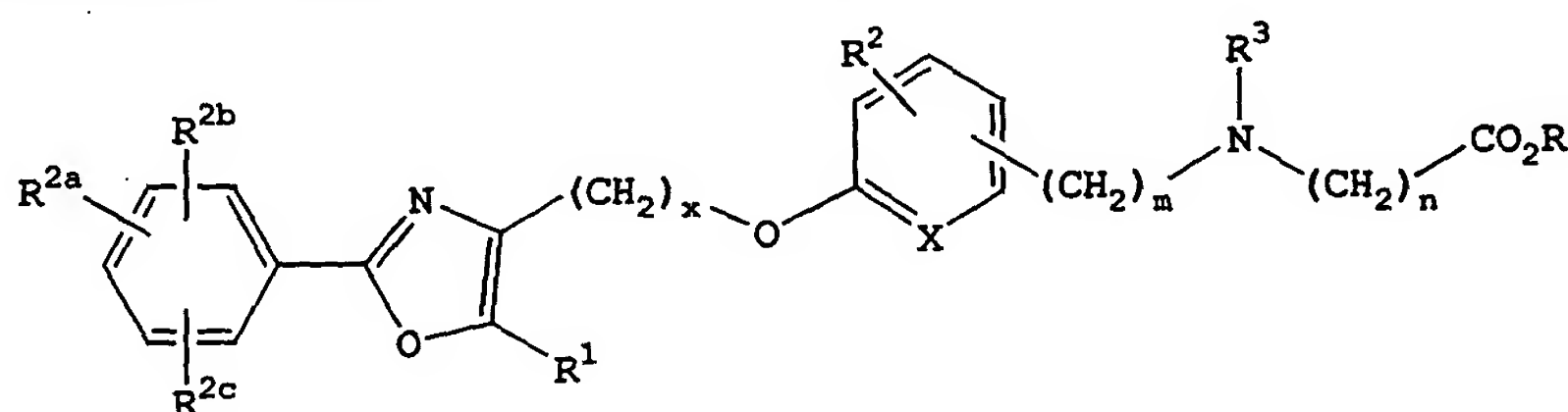
--2. (Amended) The method as defined in Claim 34 wherein the [A] compound [having] employed has the structure



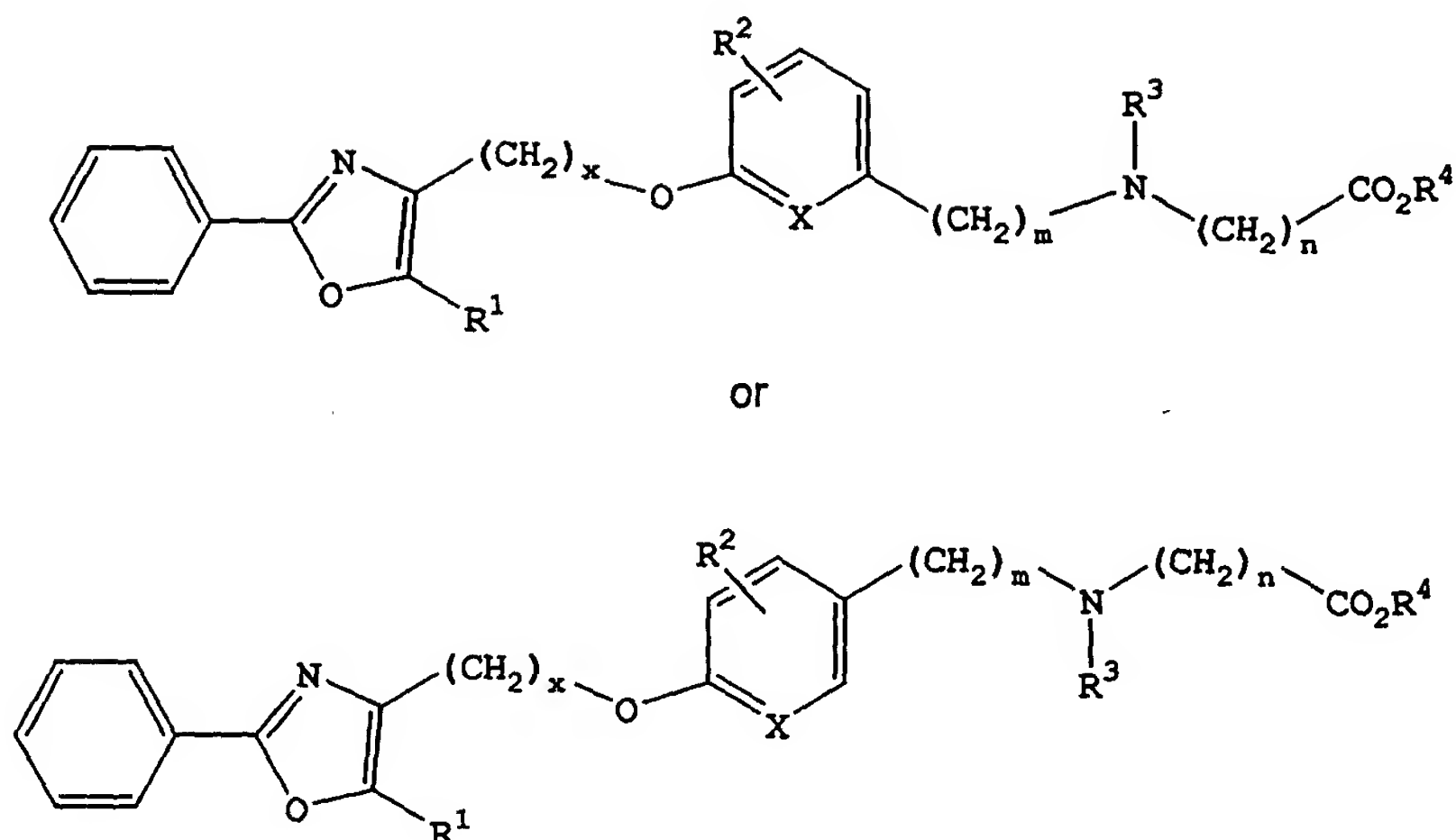
or



--3. (Amended) The [compound] method as defined in Claim [1] 34 wherein the compound employed has the [having the] structure



--4. (Amended) The [compound] method as defined in Claim [1] 34 wherein the compound employed has the [having the] structure



--5. (Amended) The [compound] method as defined in Claim [1] 34 where in the compound employed [wherein] (CH<sub>2</sub>)<sub>x</sub> is alkylene, alkenylene, allenyl, or alkynylene. --

--10. (Amended) The [compound] method as defined in Claim [1] 34 [wherein R<sup>2a</sup> is alkoxy or H,] where in the compound employed

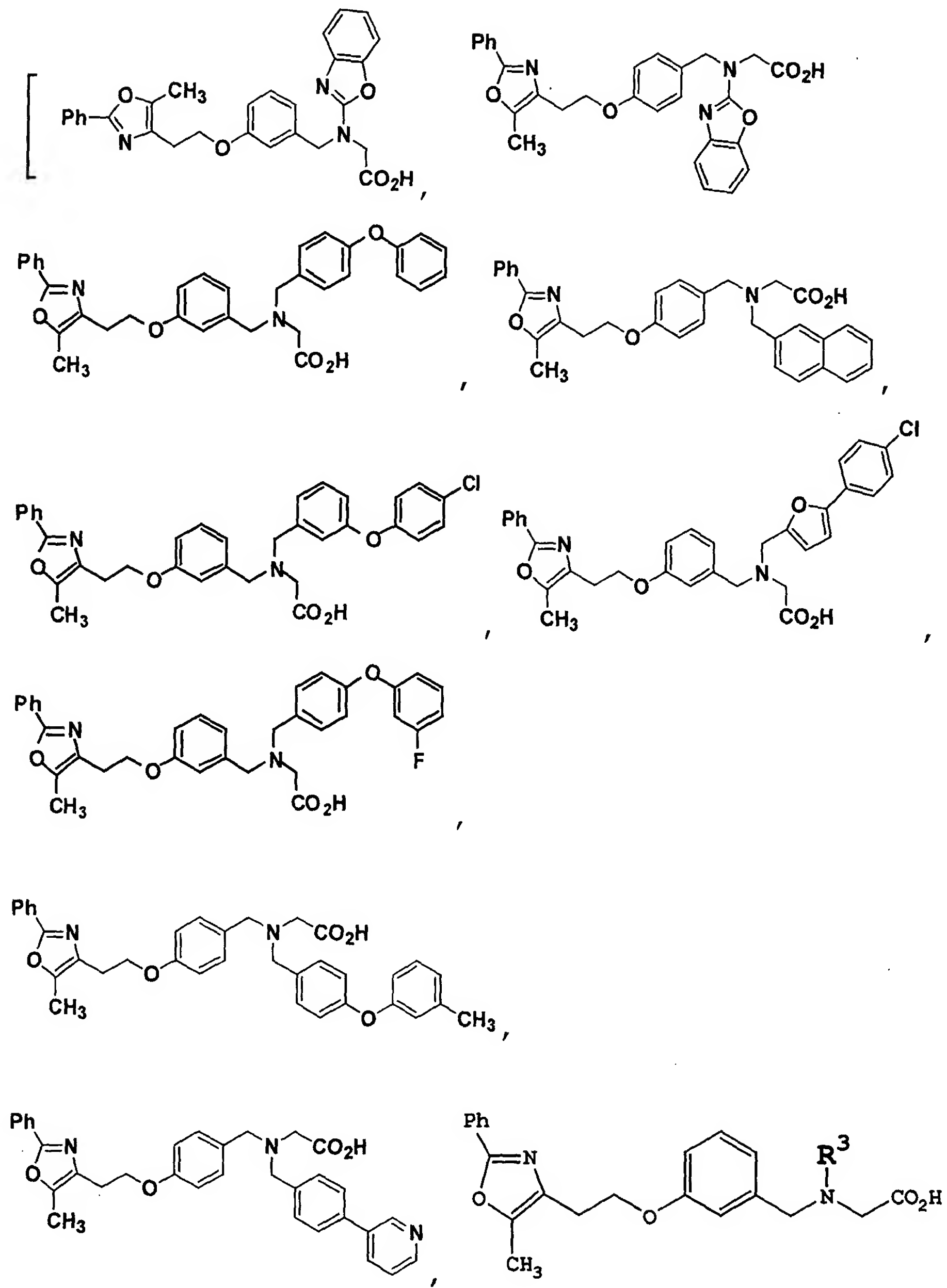
(CH<sub>2</sub>)<sub>x</sub> is CH<sub>2</sub>, (CH<sub>2</sub>)<sub>2</sub>, (CH<sub>2</sub>)<sub>3</sub>, or  $\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \diagdown \quad \diagup \\ \text{C} \end{array}$ , (CH<sub>2</sub>)<sub>m</sub> is CH<sub>2</sub>, or  $\begin{array}{c} \text{R}_a \\ | \\ \text{CH} \end{array}$  [(where R<sub>a</sub> is alkyl or alkenyl)], (CH<sub>2</sub>)<sub>n</sub> is CH<sub>2</sub>, R<sup>1</sup> is lower alkyl, [preferably -CH<sub>3</sub>,] R<sup>2</sup> is H, R<sup>2a</sup> is H, R<sup>4</sup> is H, [X is CH,] and R<sup>3</sup> is arylalkyloxycarbonyl, [arylheteroarylalkyl, aryloxyarylalkyl, arylalkyl,] aryloxycarbonyl, haloaryl-oxycarbonyl, alkoxyaryloxycarbonyl, alkylaryloxycarbonyl, aryloxyaryloxycarbonyl, heteroaryloxyarylalkyl, heteroaryloxycarbonyl, [aryloxyarylcarbonyl,] arylalkenyloxycarbonyl, cycloalkylaryloxycarbonyl, [arylalkylarylcarbonyl, heteroaryl-heteroarylalkyl,] cycloalkyloxyaryloxycarbonyl, [heteroaryl-heteroarylcarbonyl,] alkyloxyaryloxycarbonyl, arylalkylsulfonyl, arylalkenylsulfonyl, [alkoxyarylalkyl,] arylthiocarbonyl, cycloheteroalkylalkyloxycarbonyl, cycloheteroalkyloxycarbonyl, or polyhaloalkylaryloxycarbonyl, which may be optionally substituted.--

--14. (Amended) The [compound] method as defined in Claim [1] 34 wherein the compound employed has the [having the] structure


$$\begin{array}{c} \text{CH}_3 \\ | \\ \text{CH} \end{array}$$

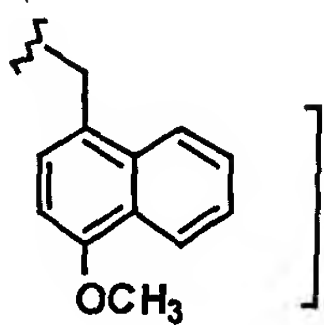
compound employed has

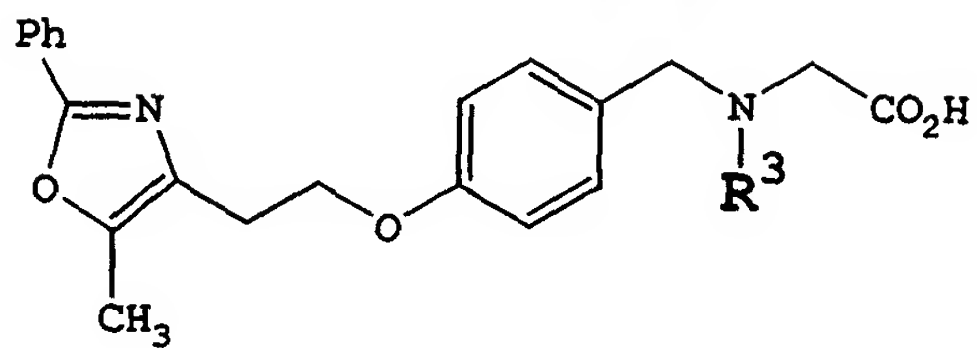
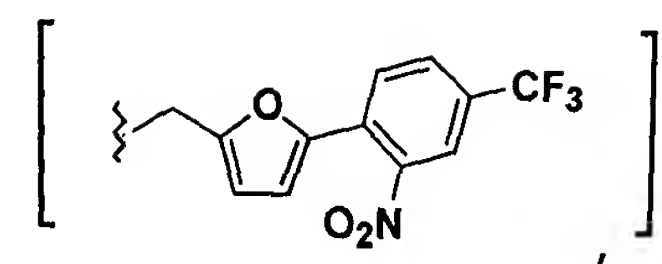




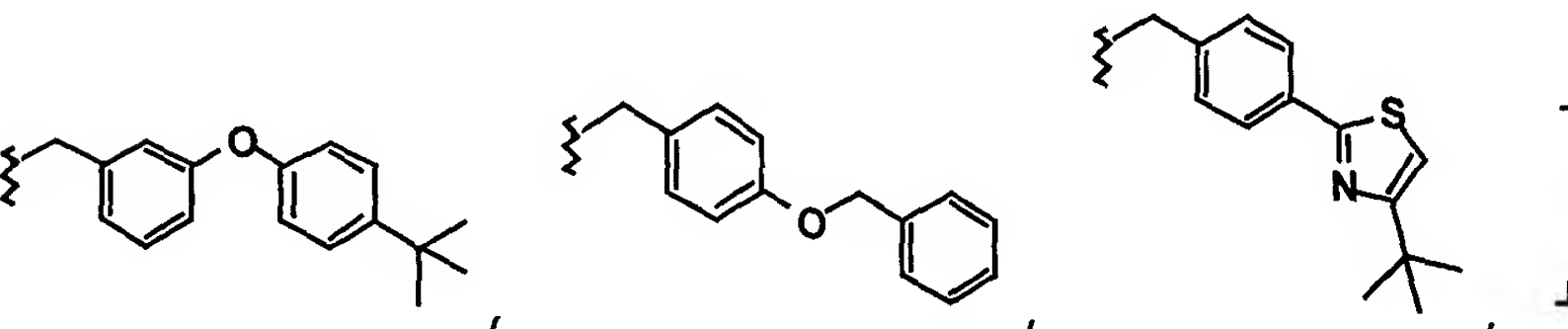
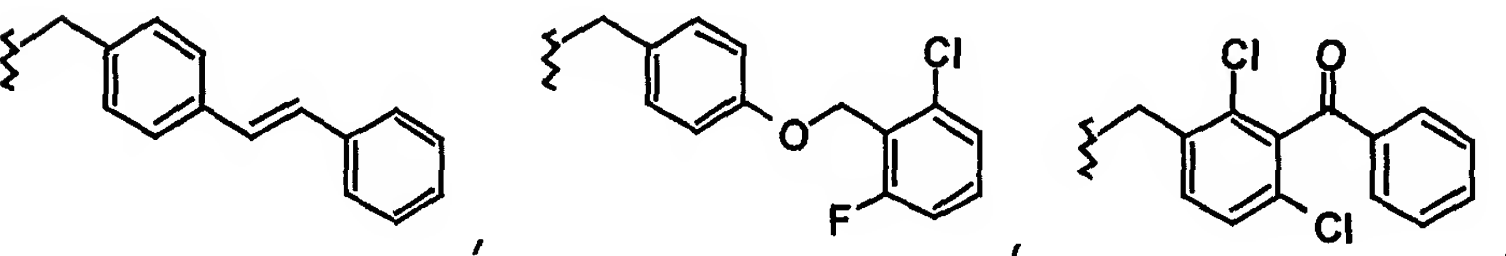
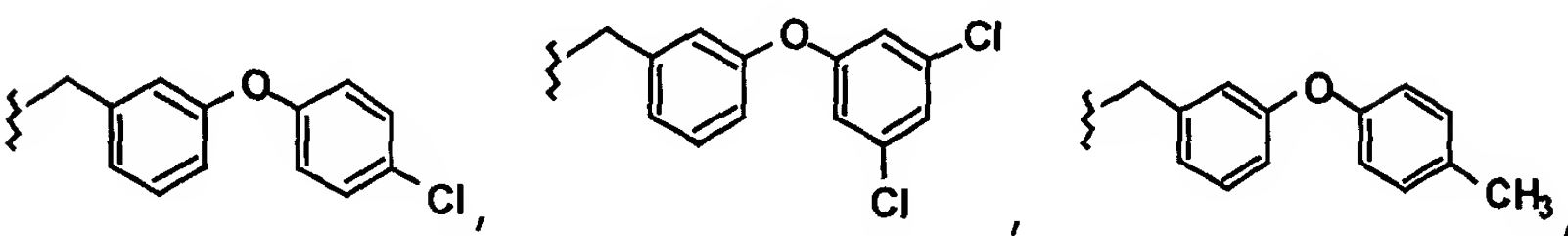
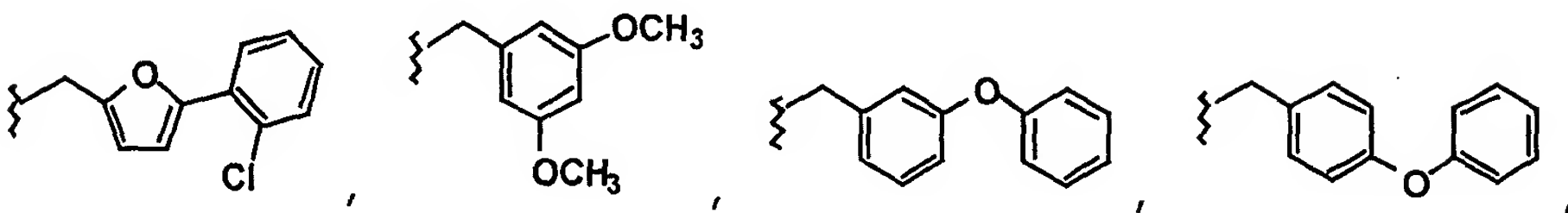
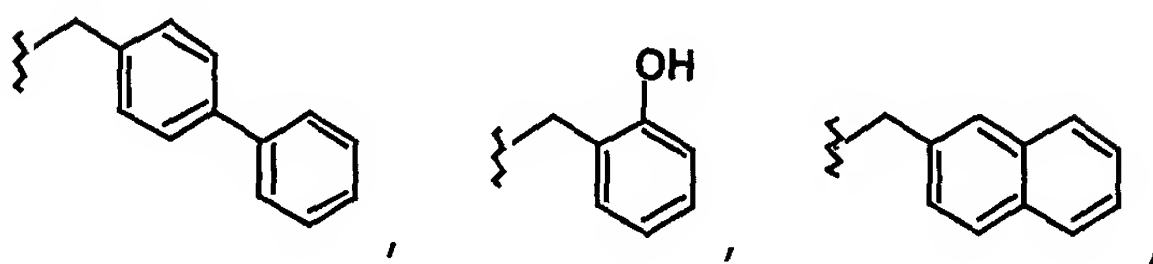
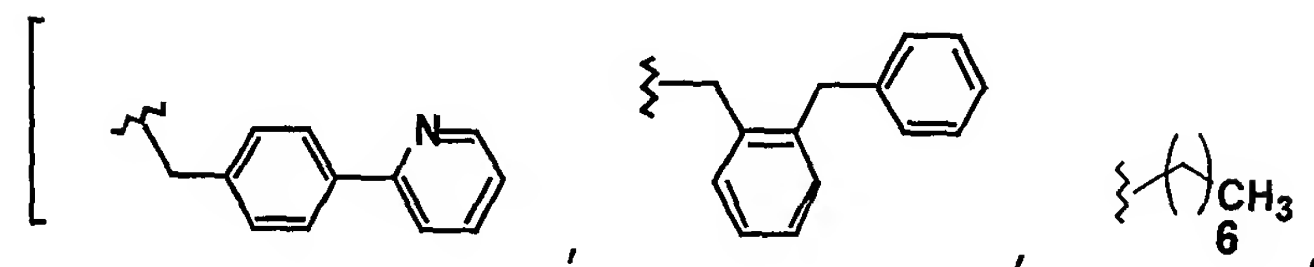
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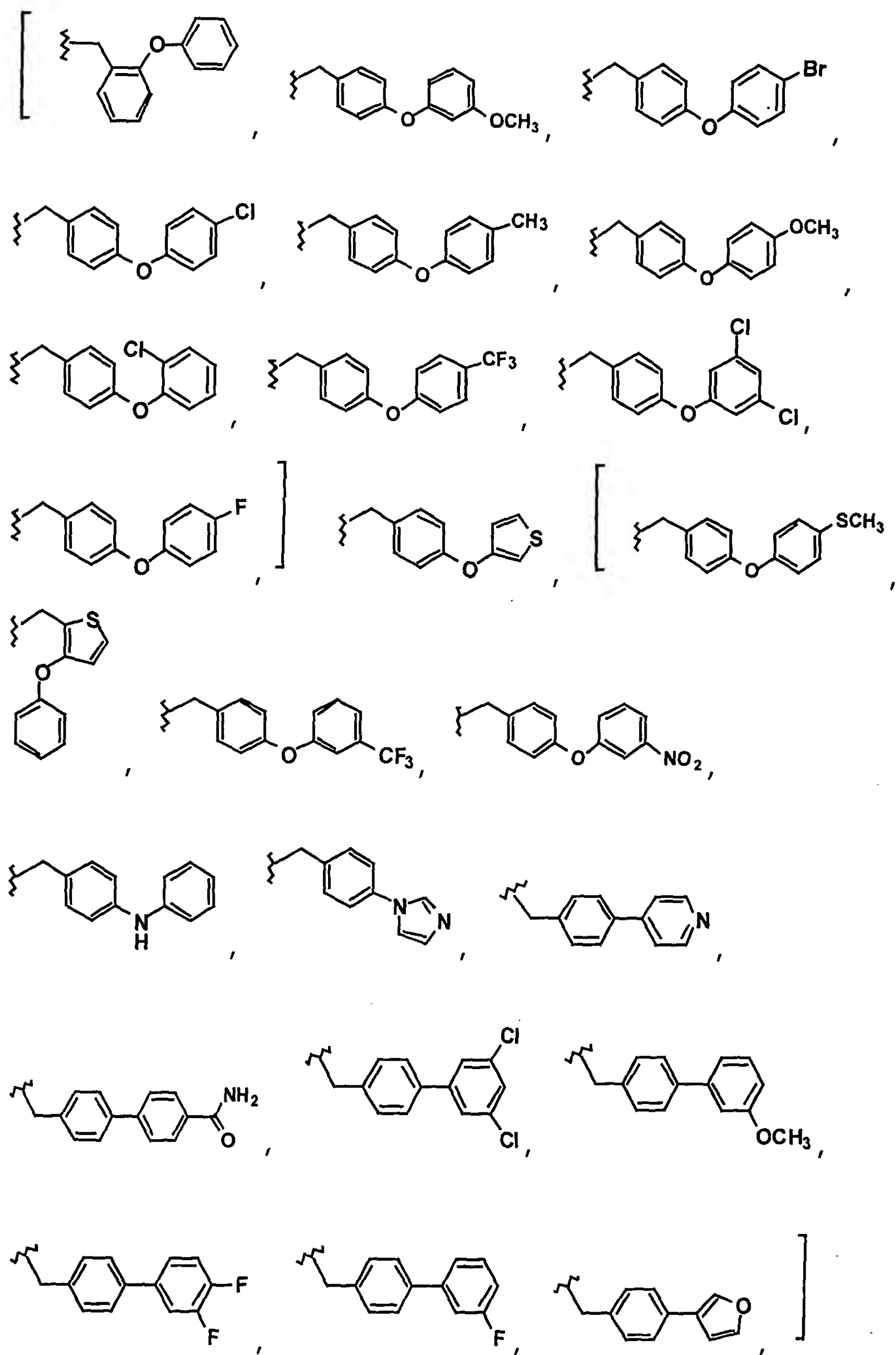


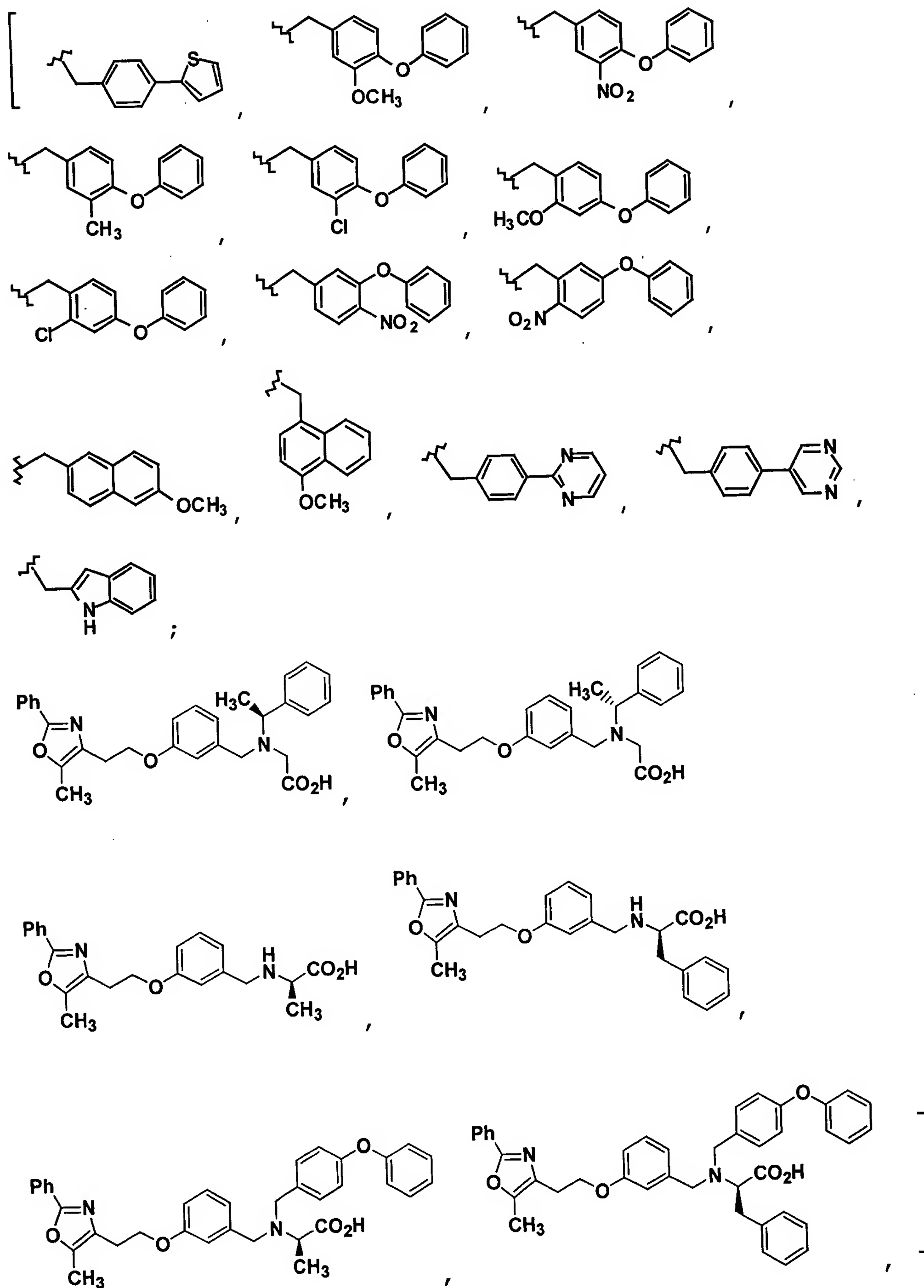


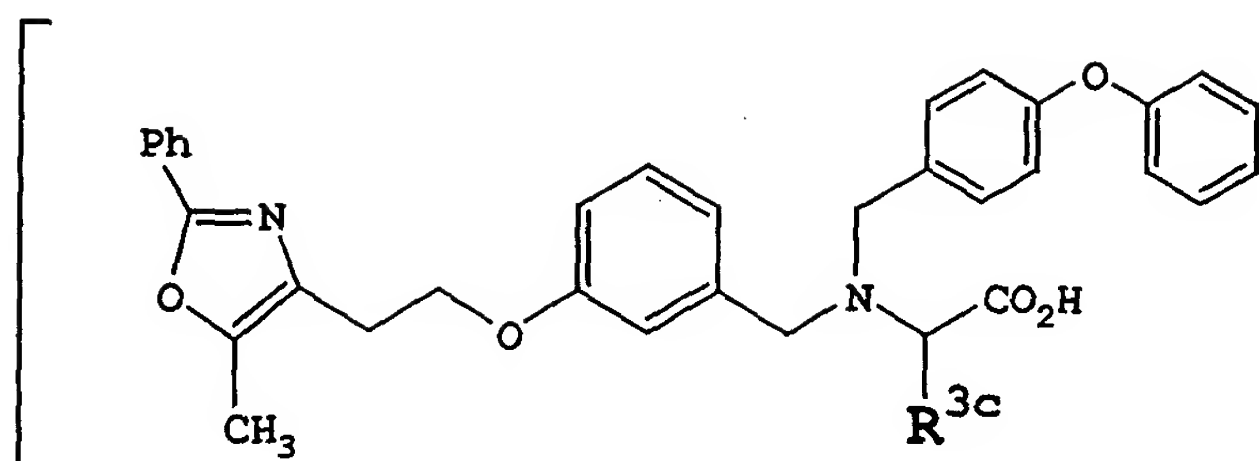
, where  $\text{R}^3 =$



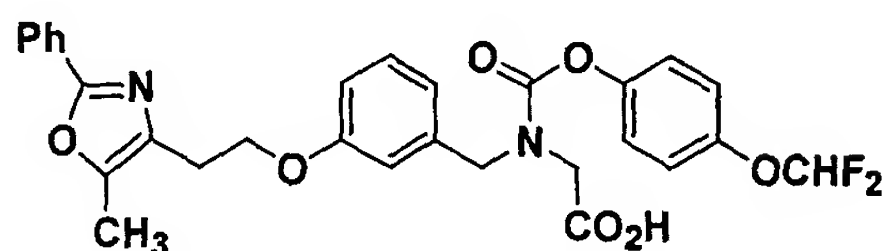
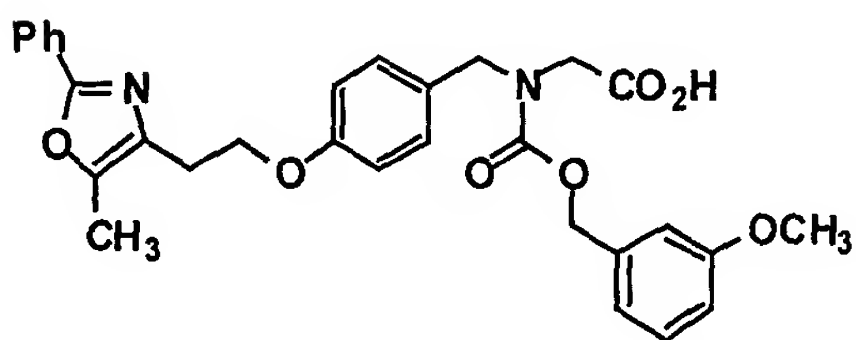
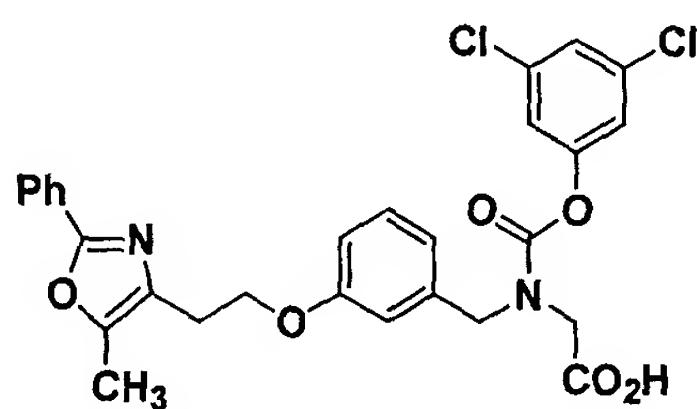
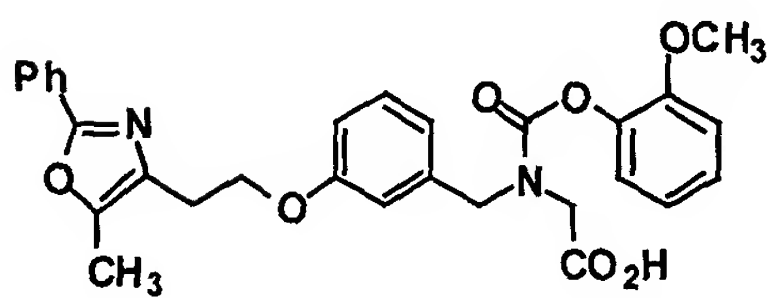
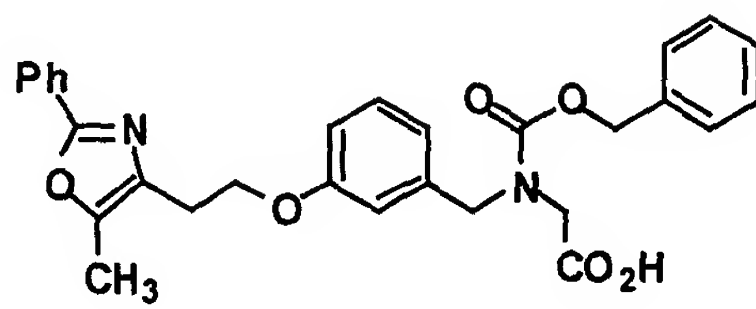
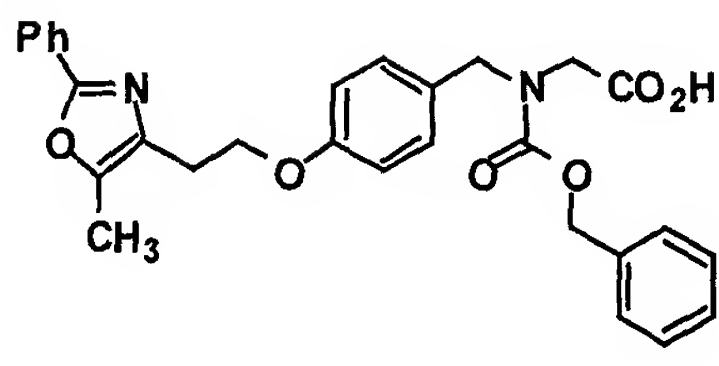
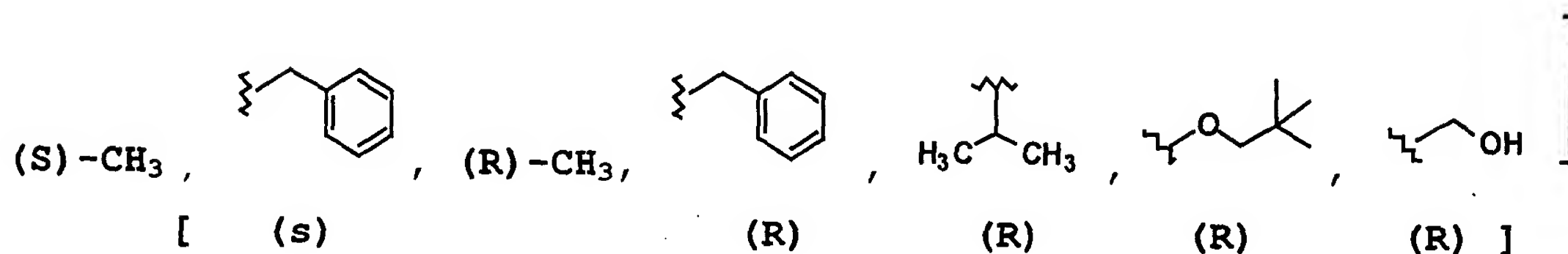


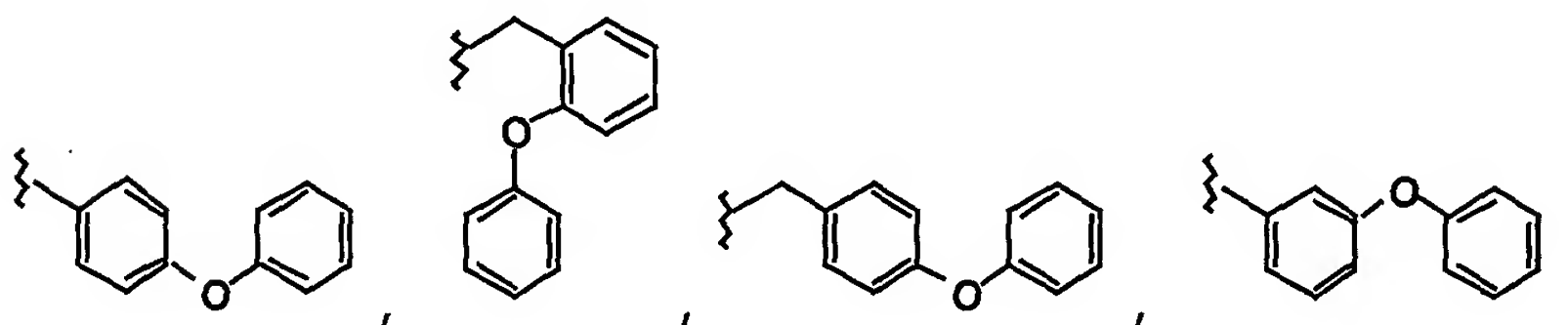


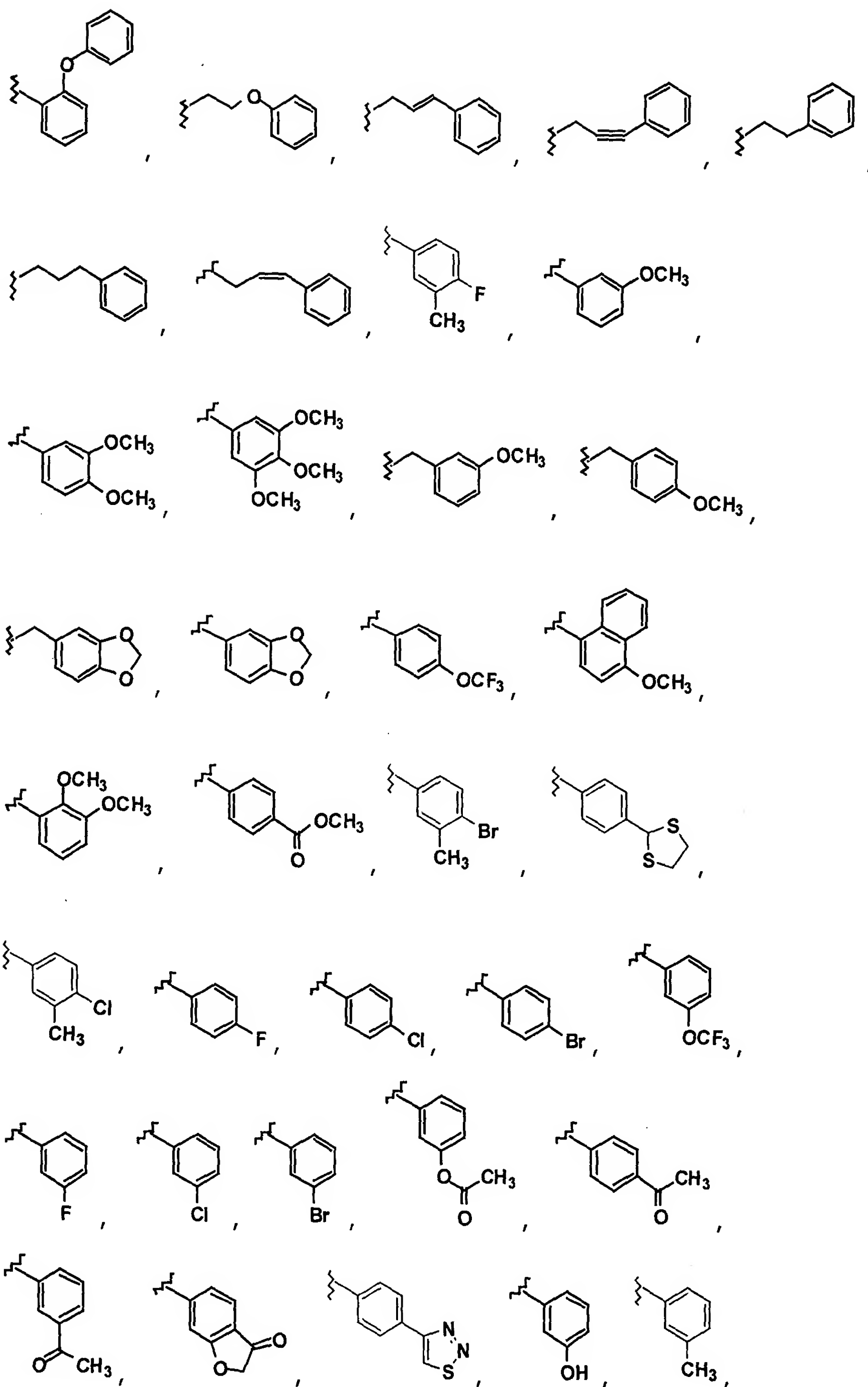


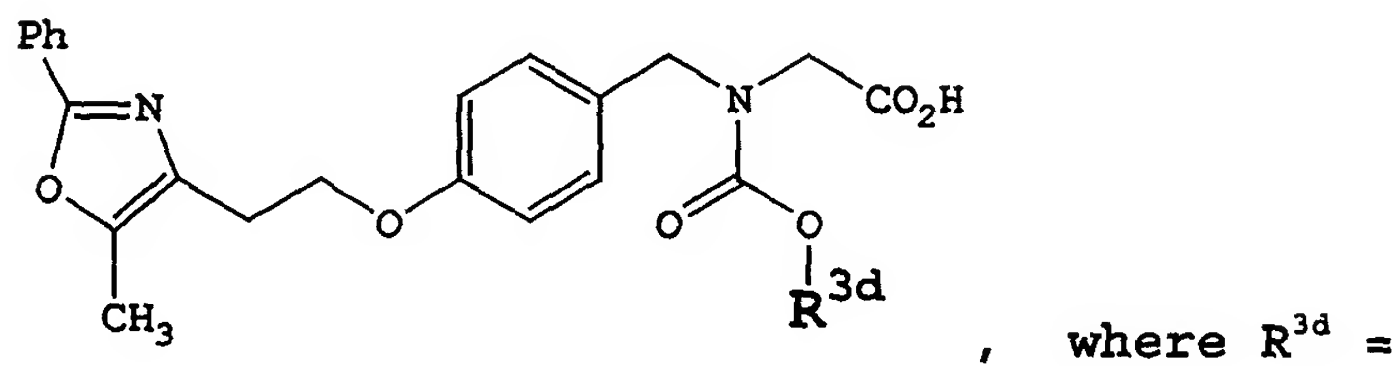


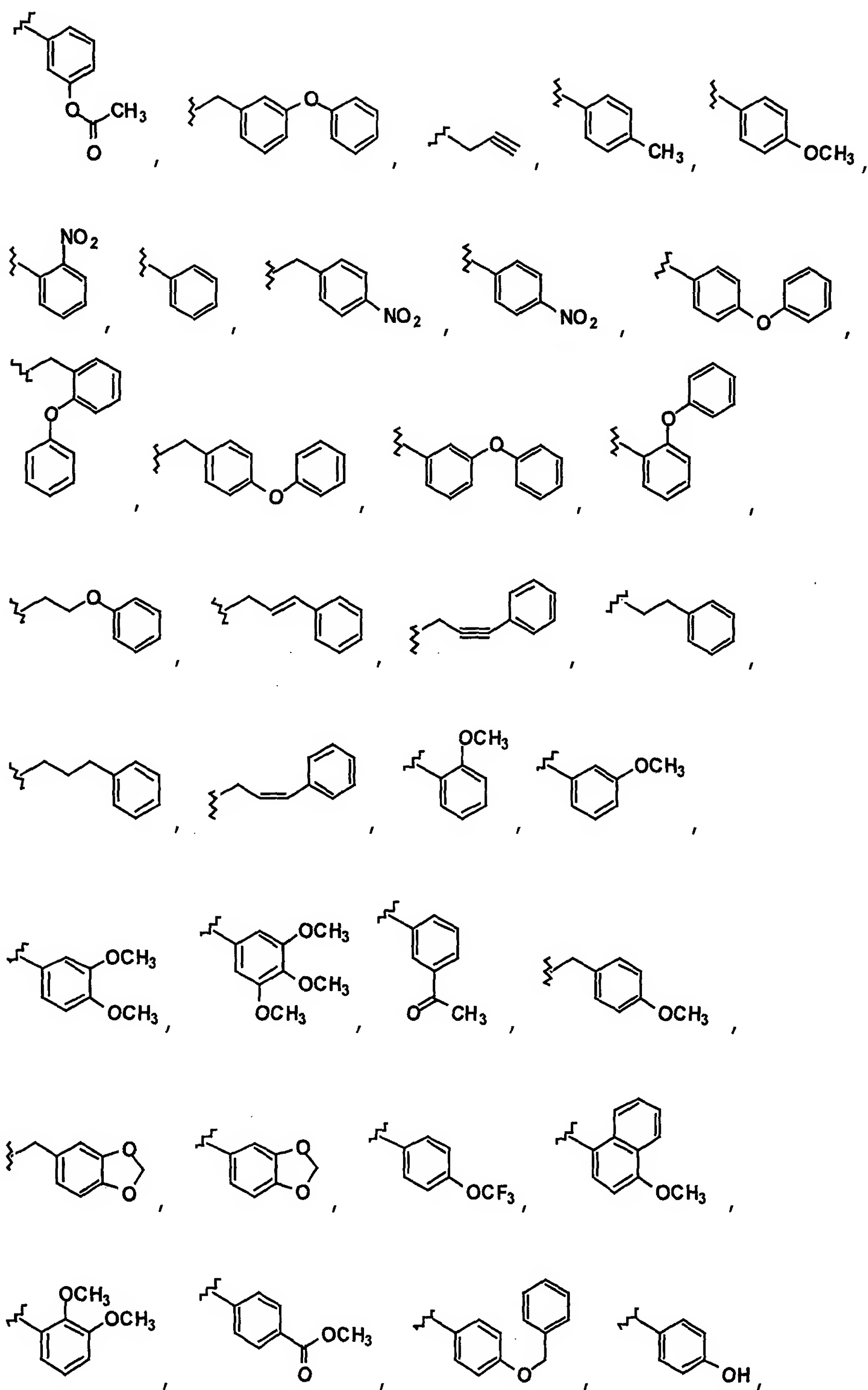
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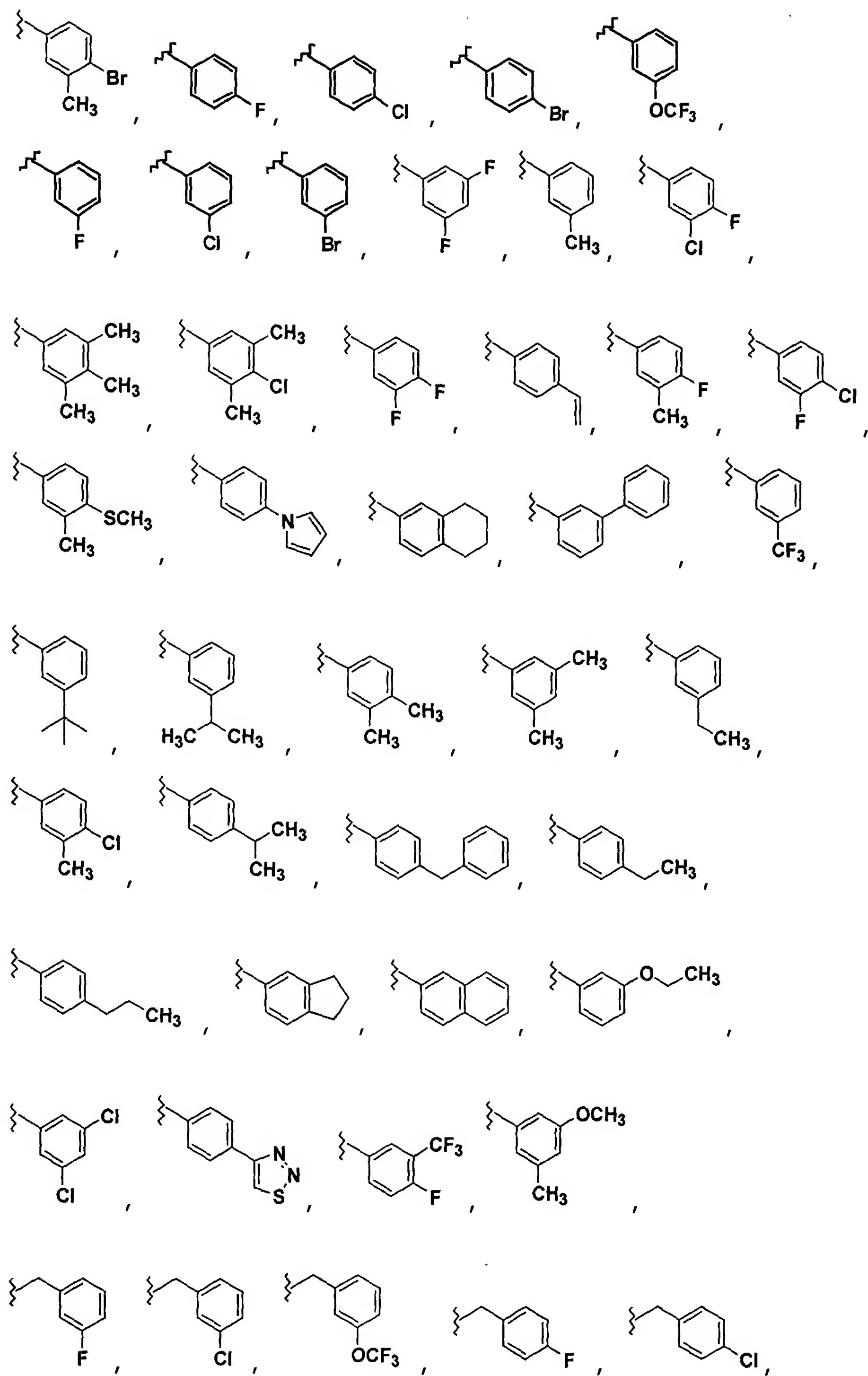




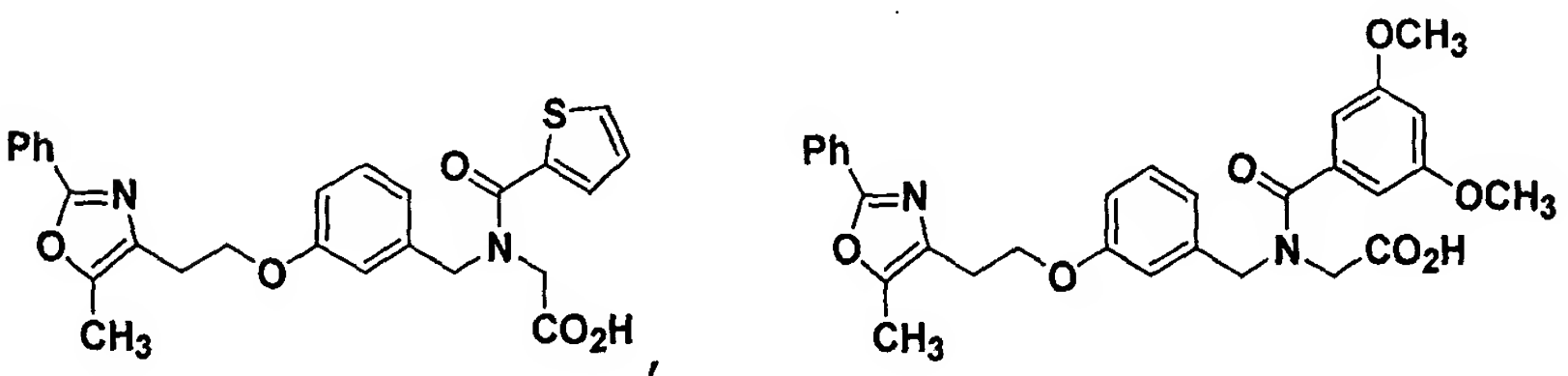
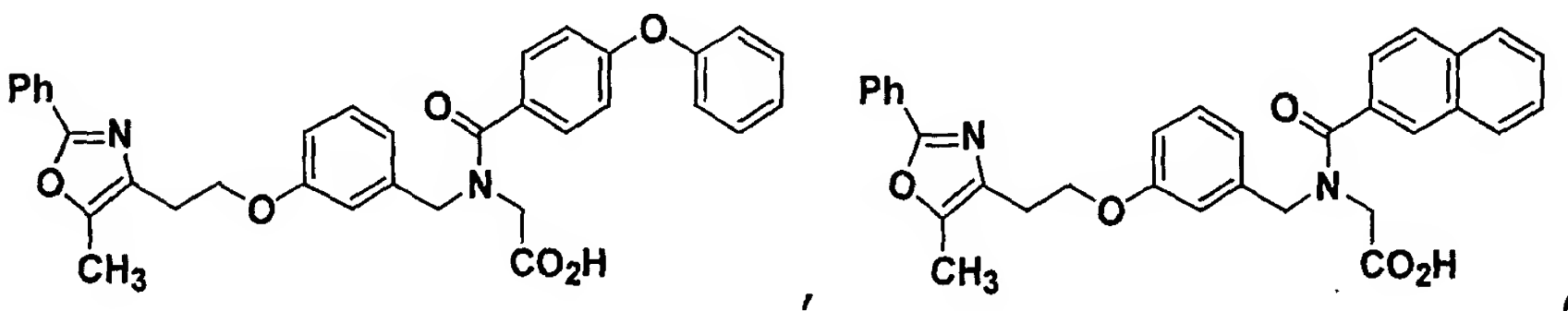
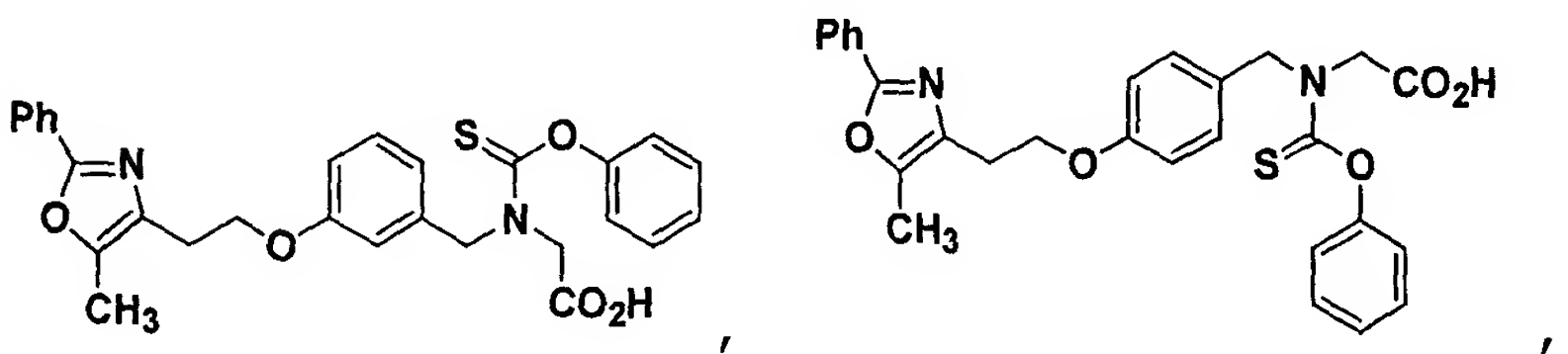
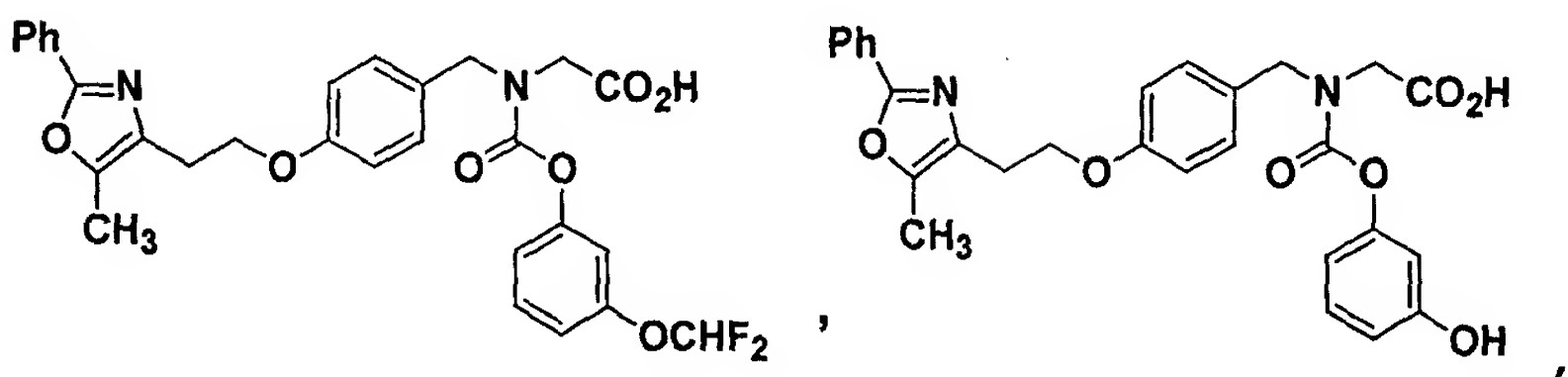
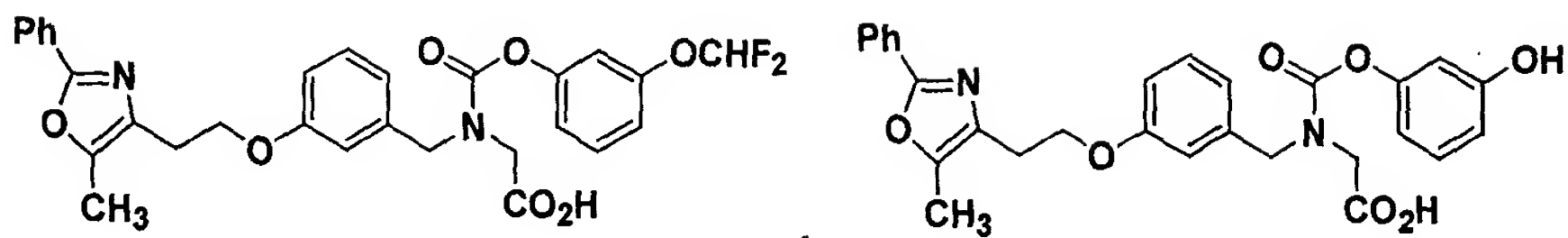
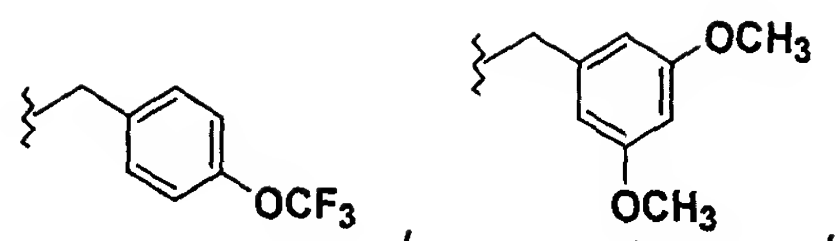


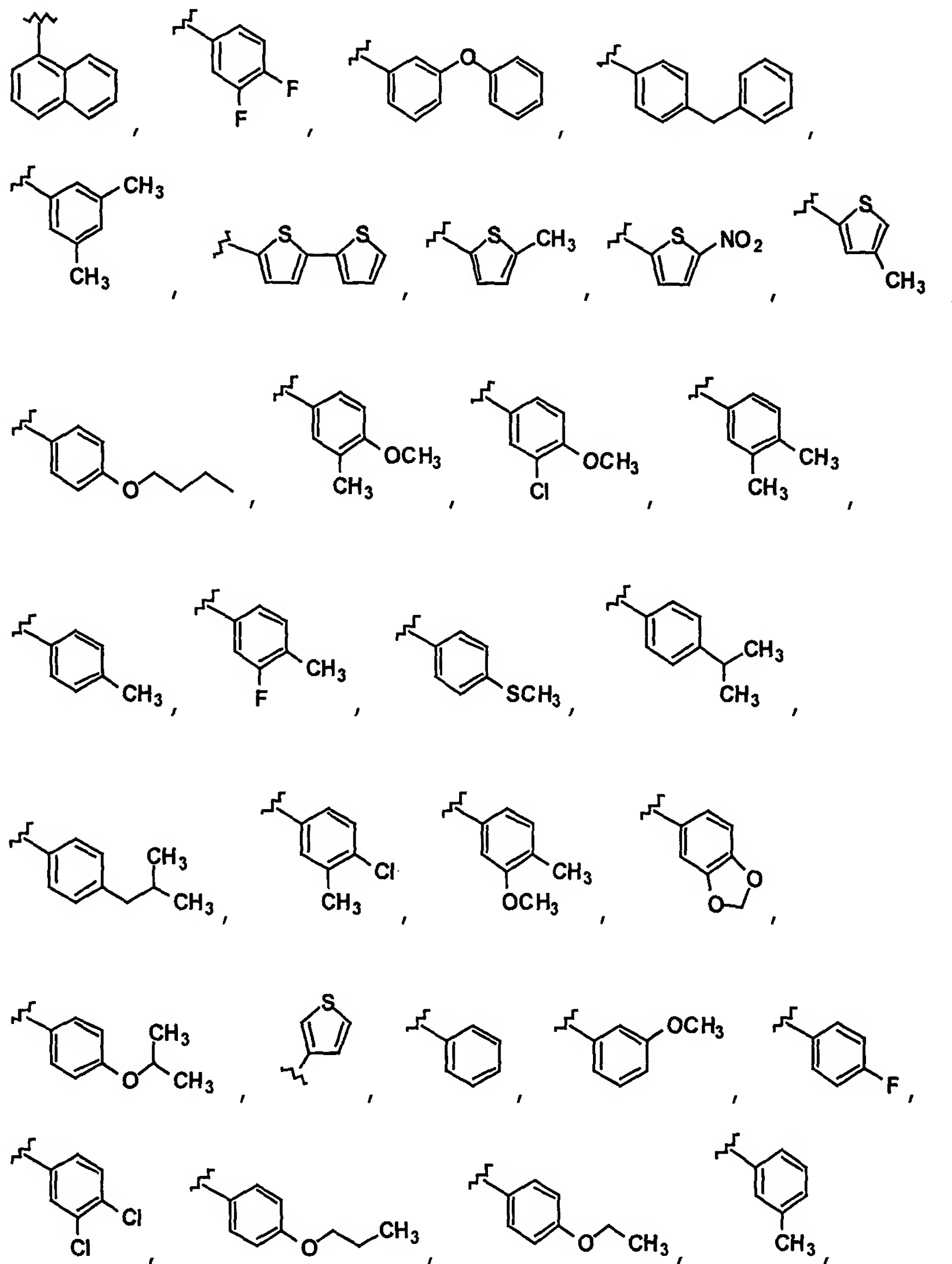
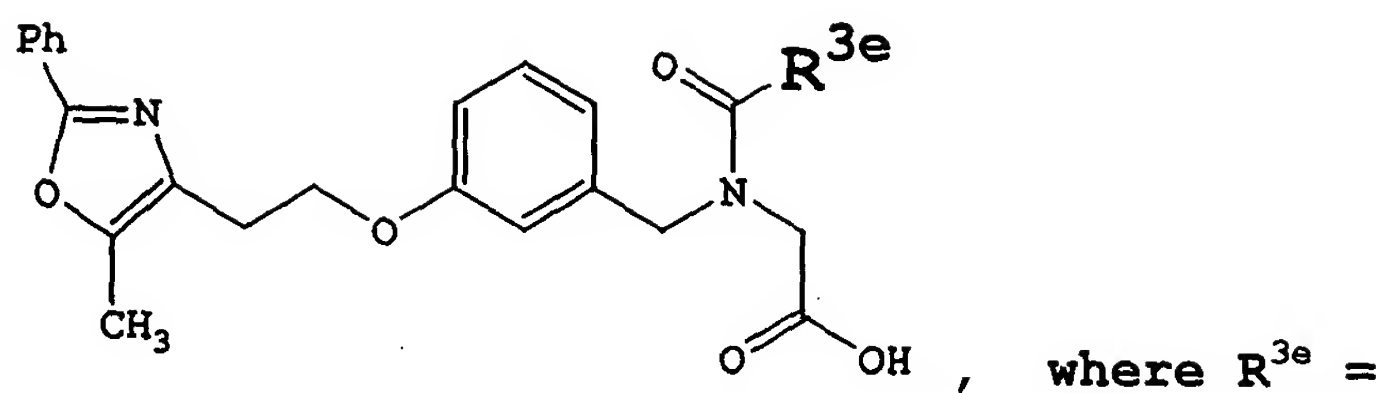


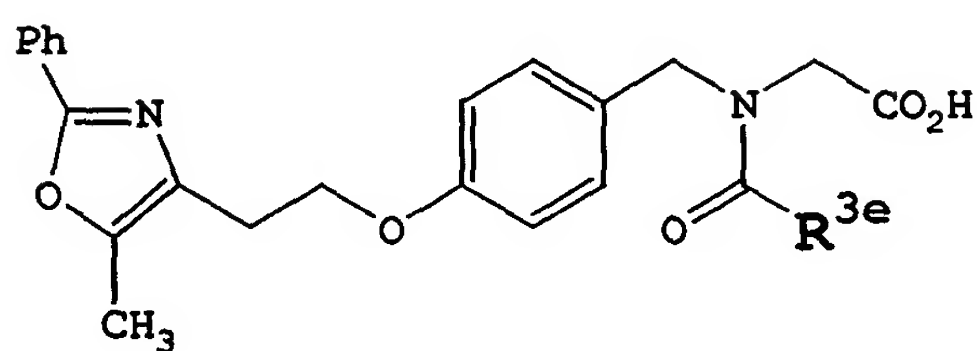
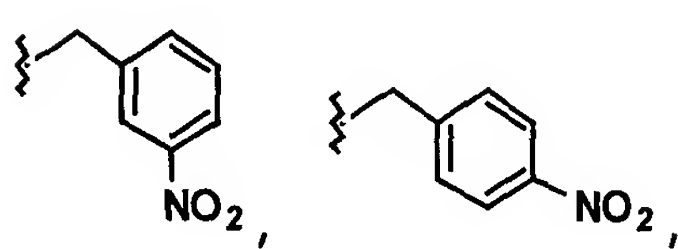
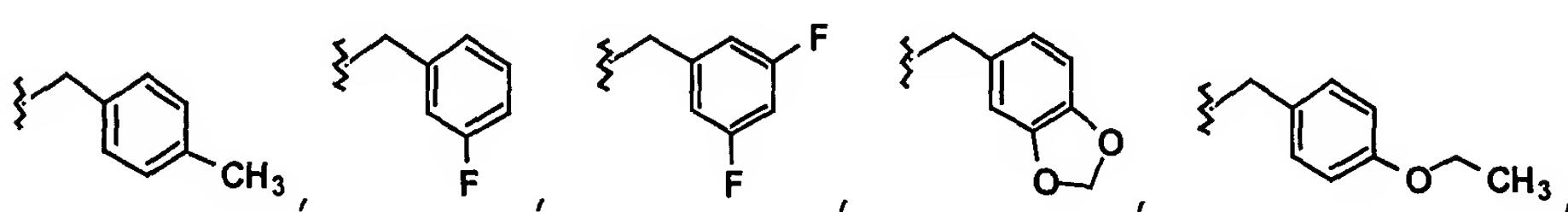
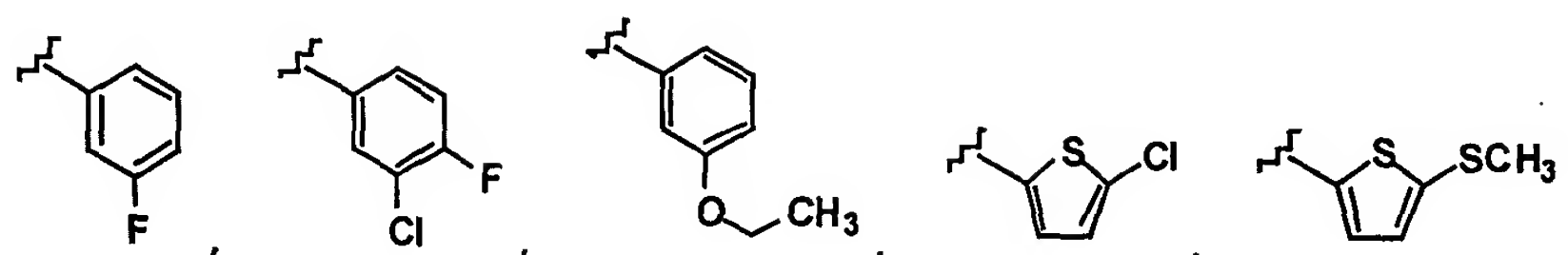
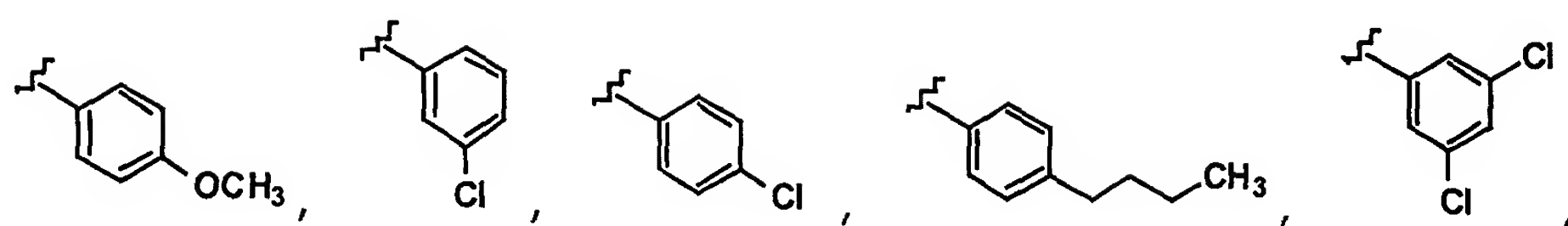




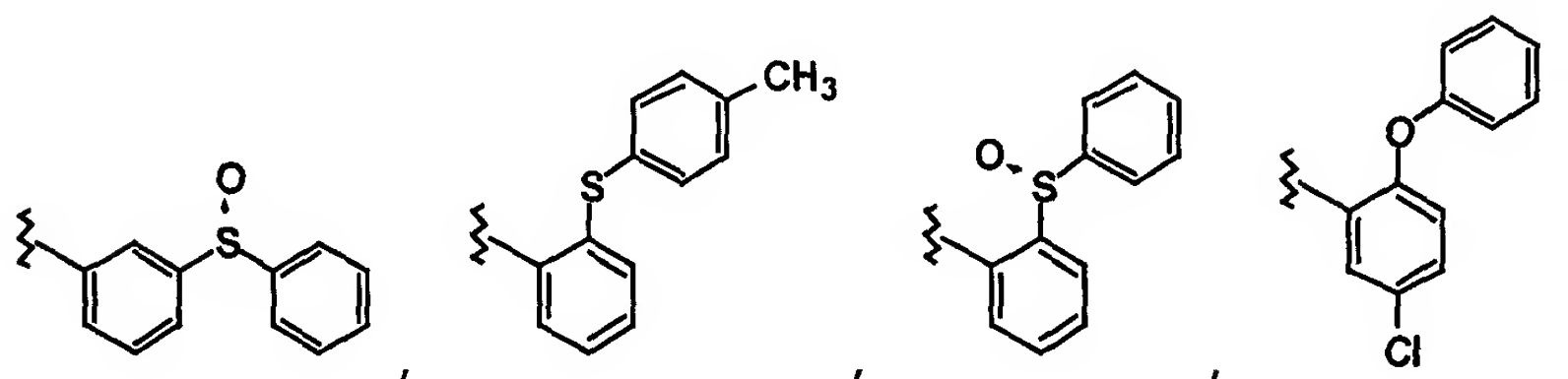
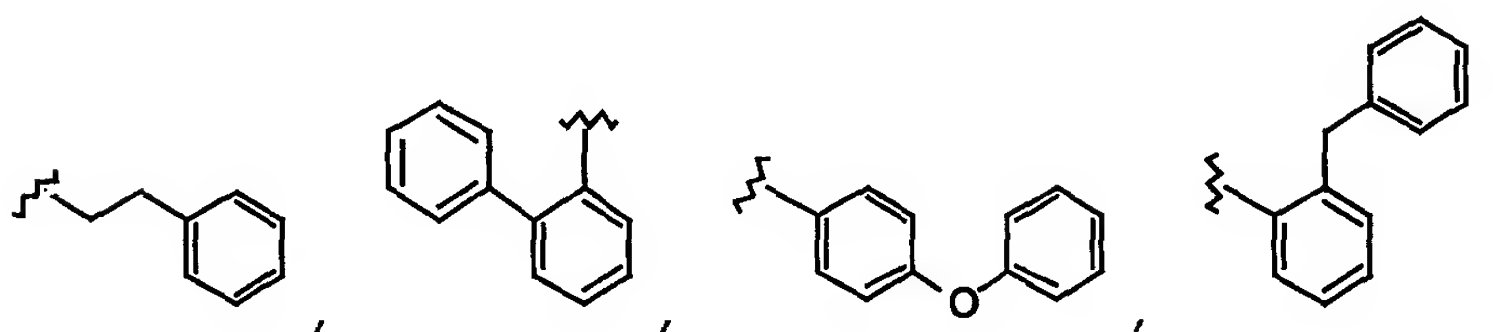




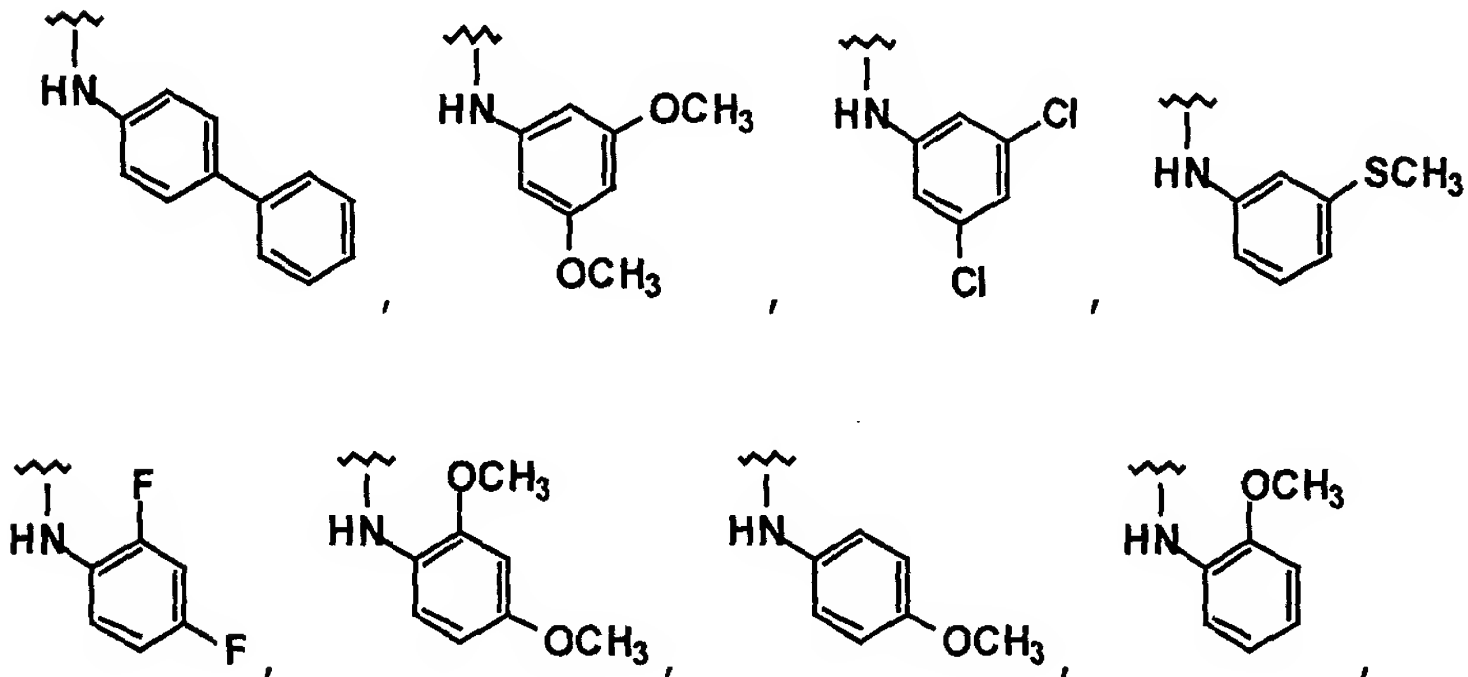
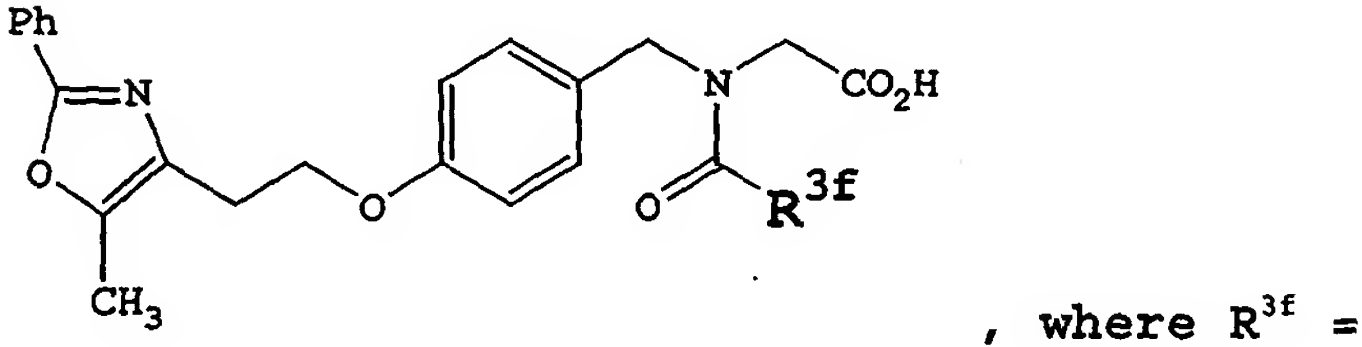
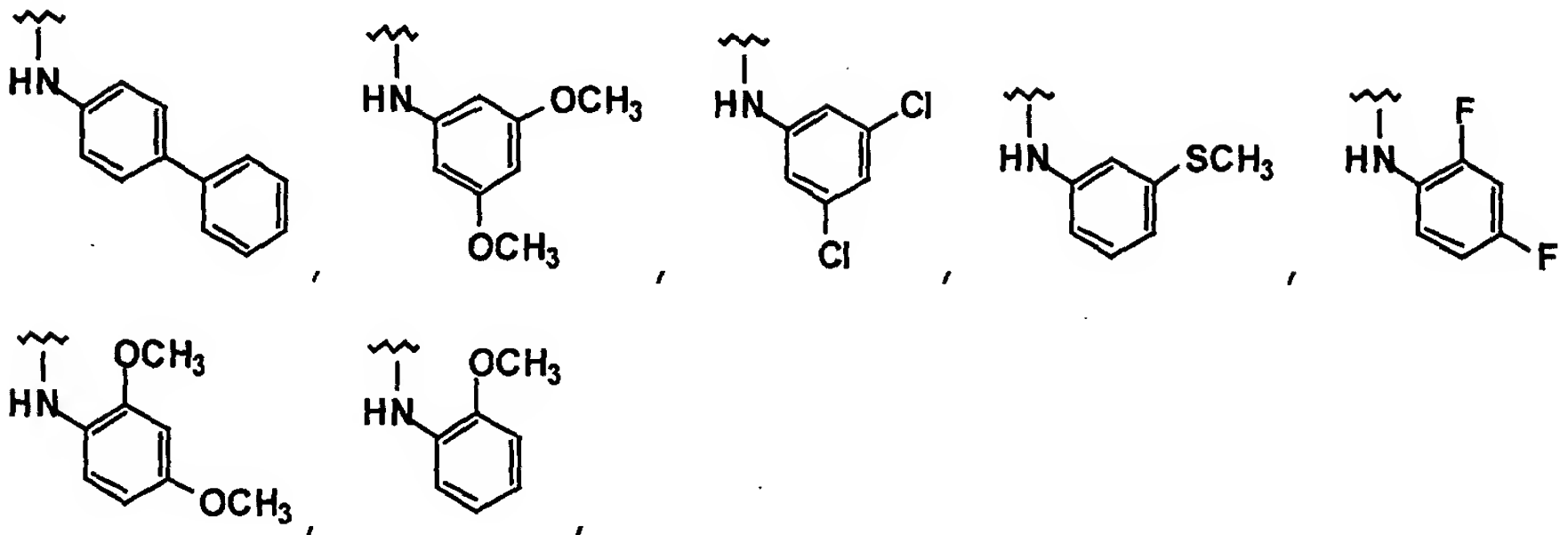
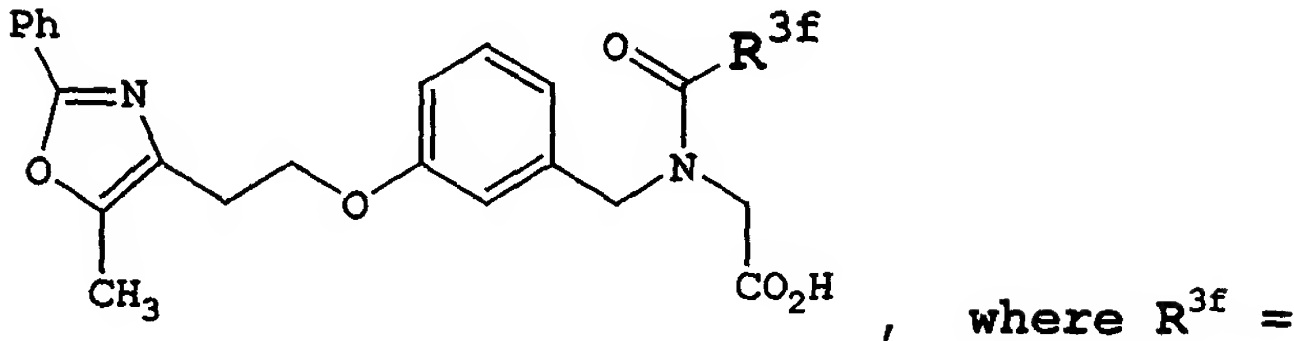
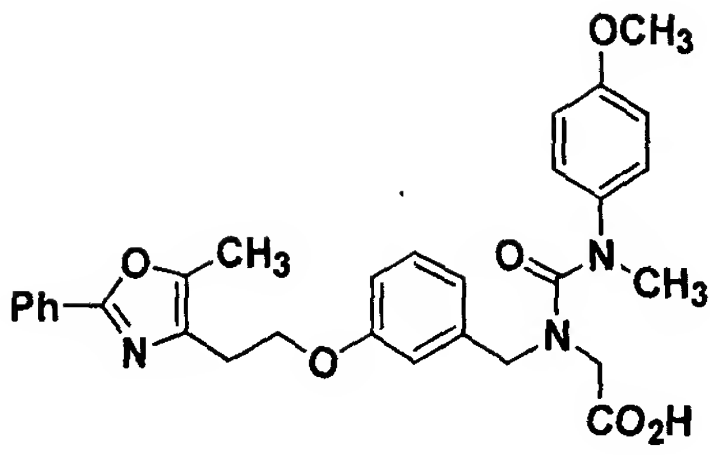


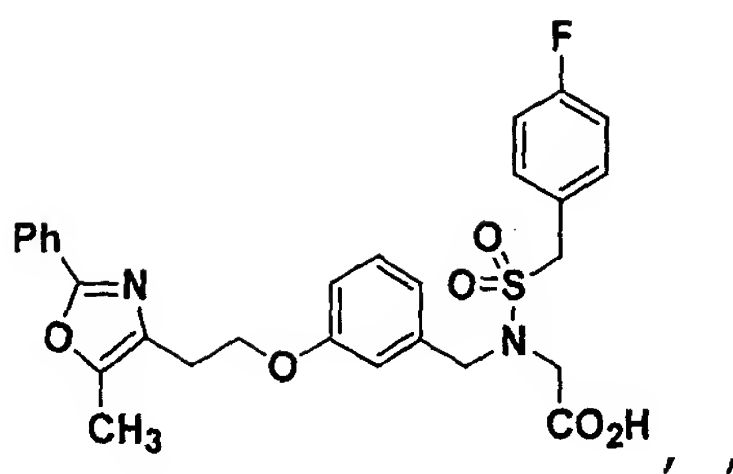


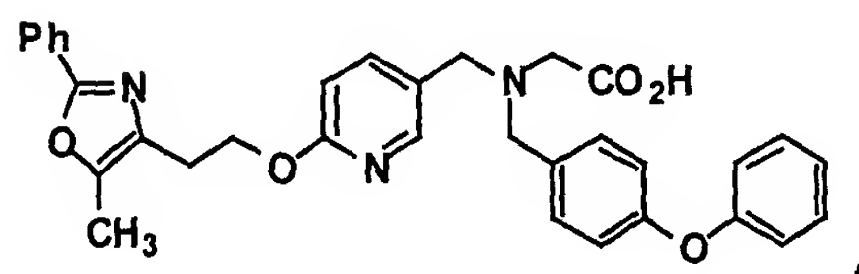
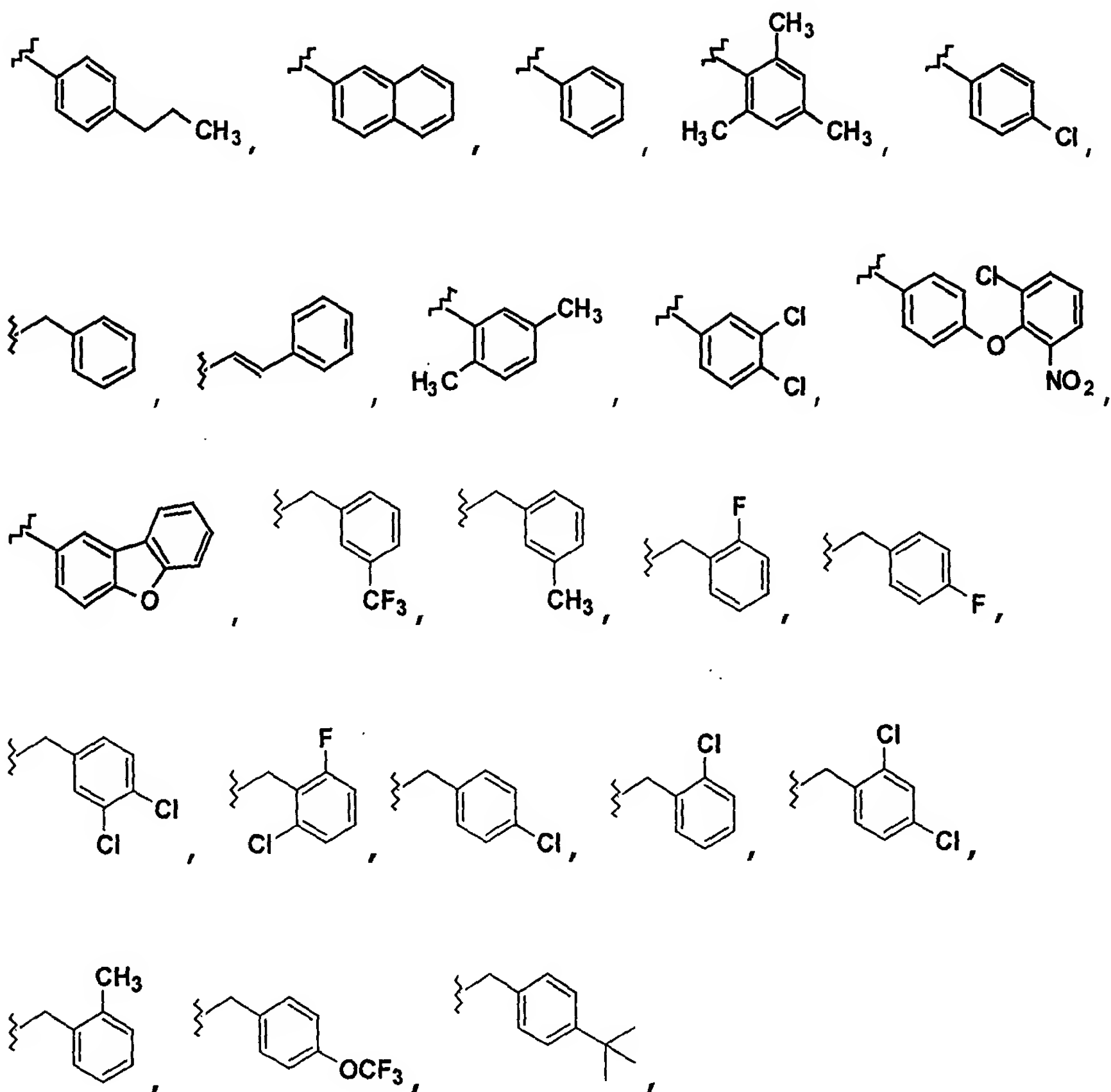
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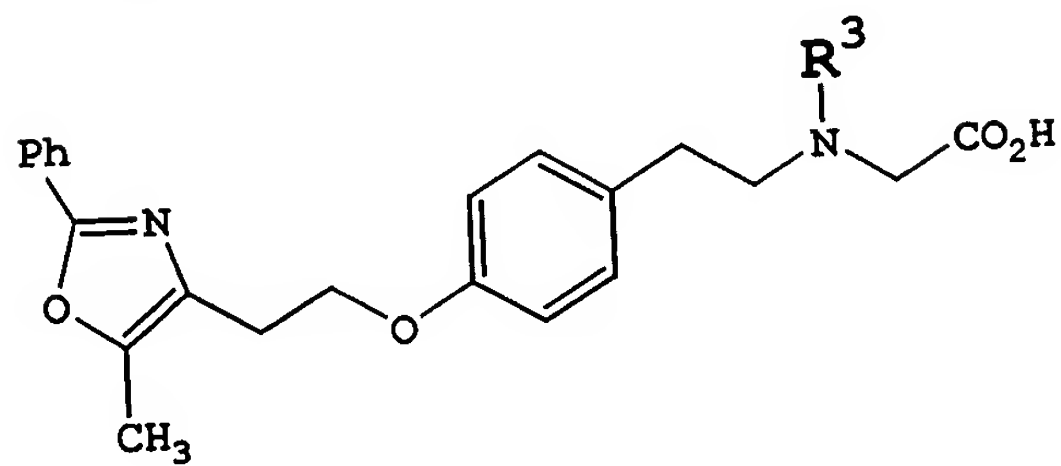
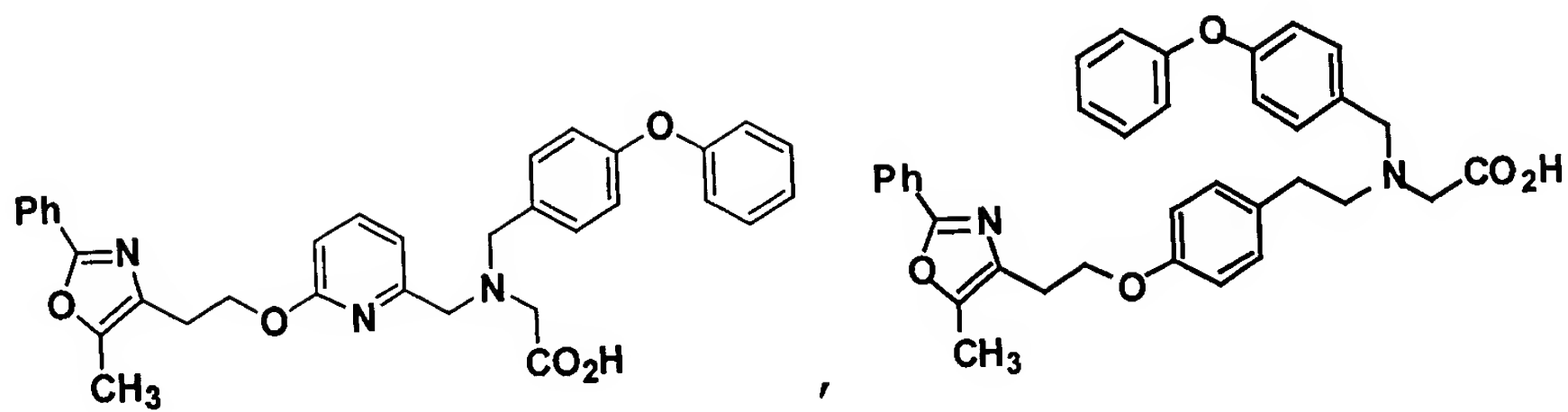




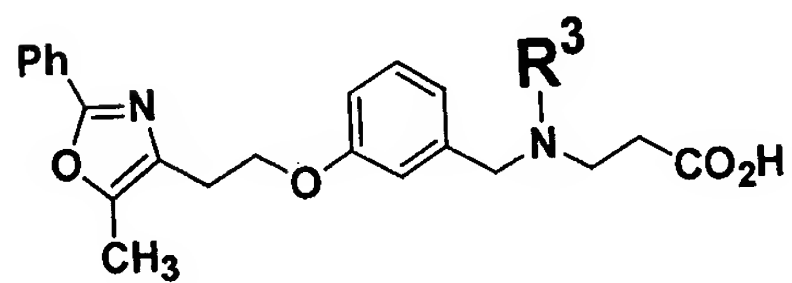
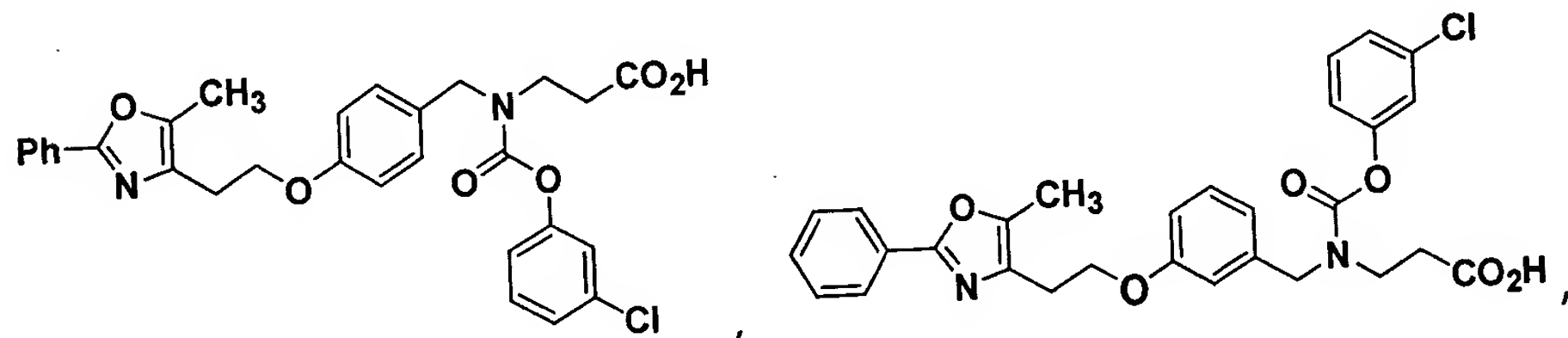
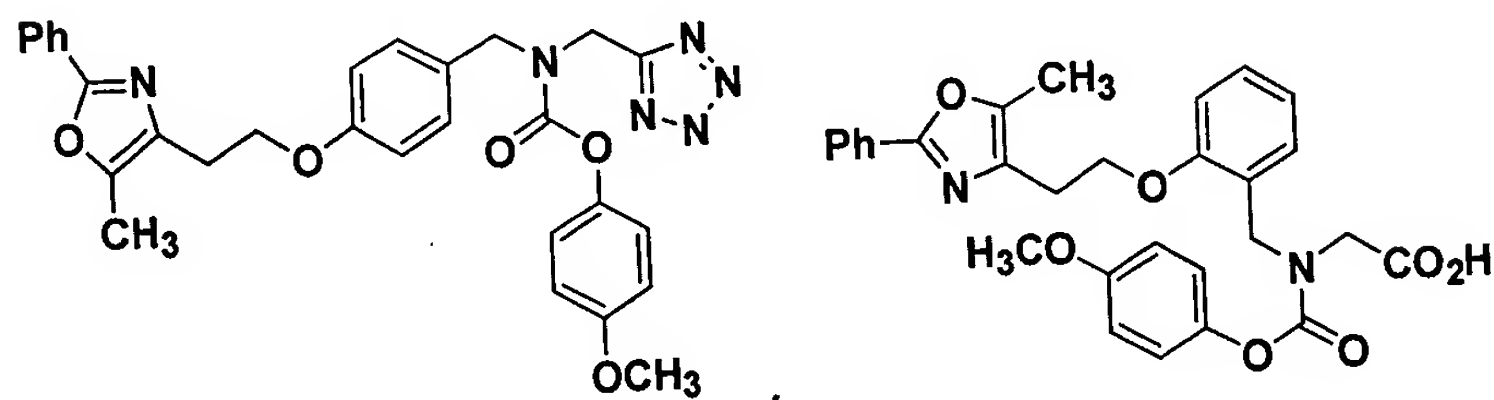
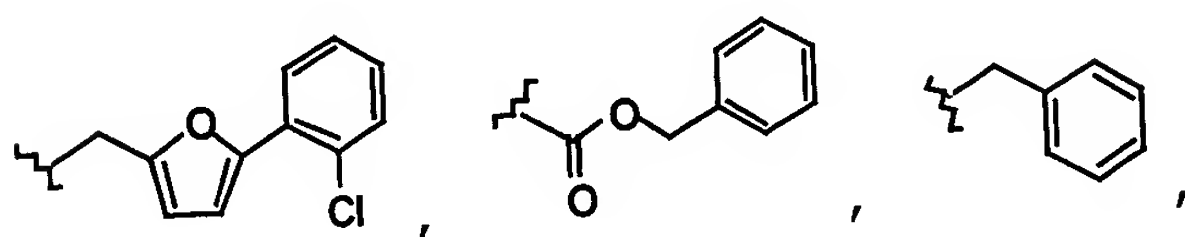




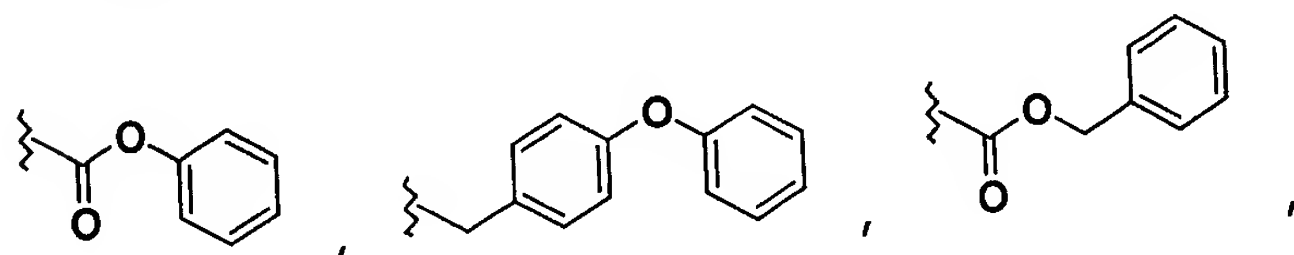




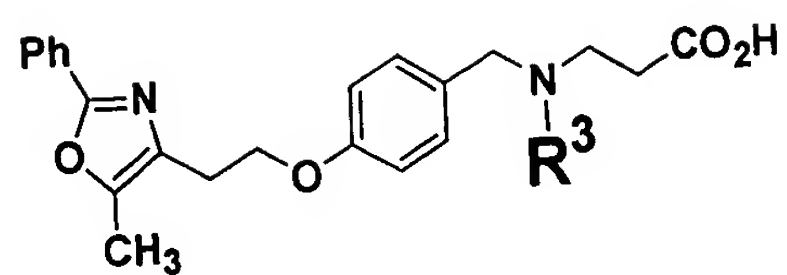
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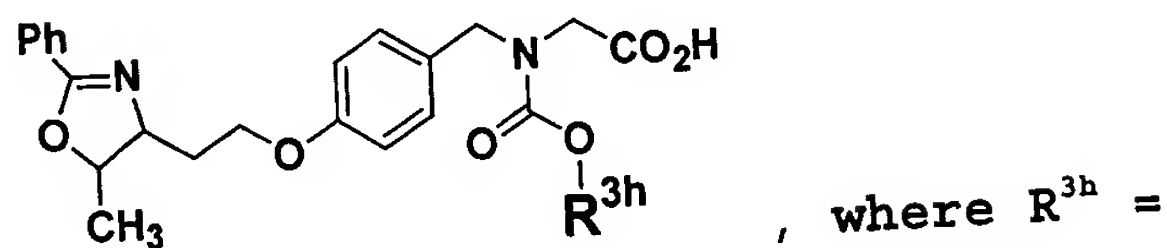
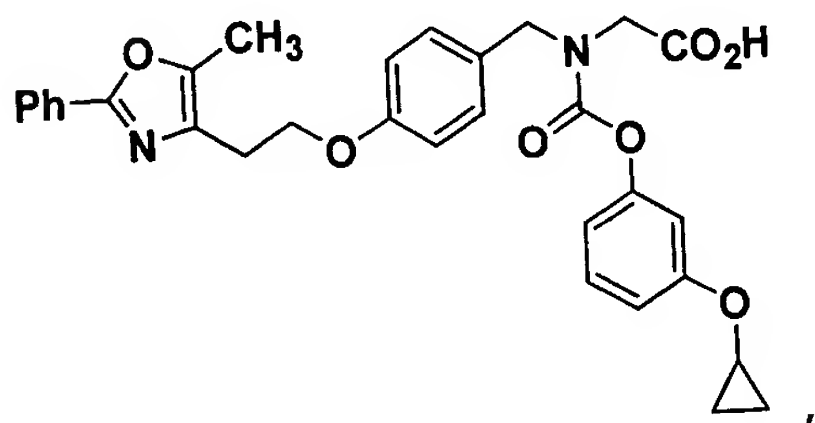
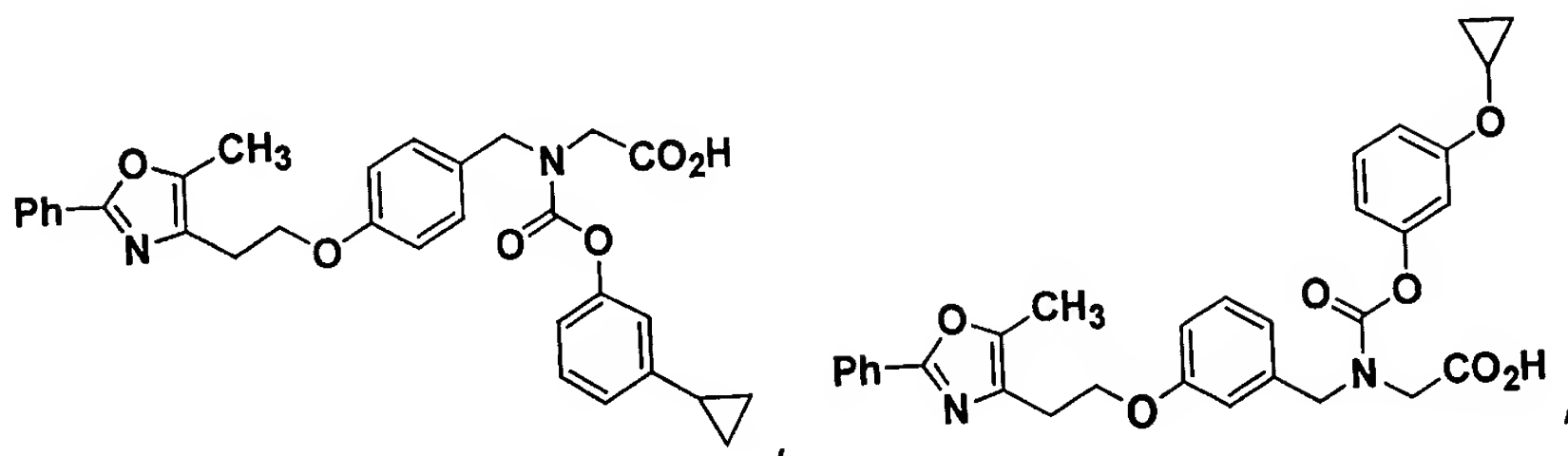
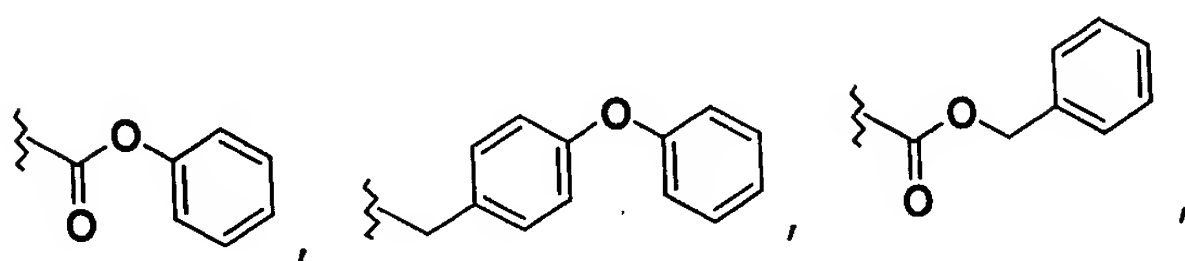
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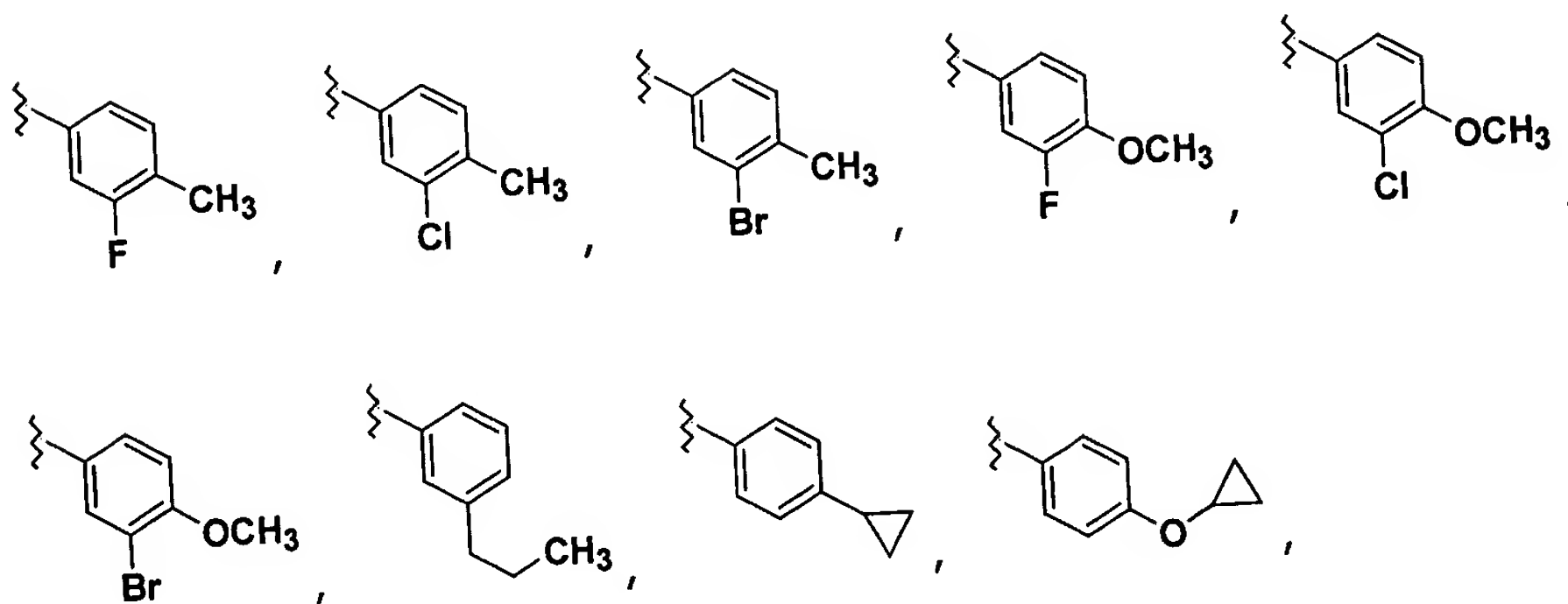


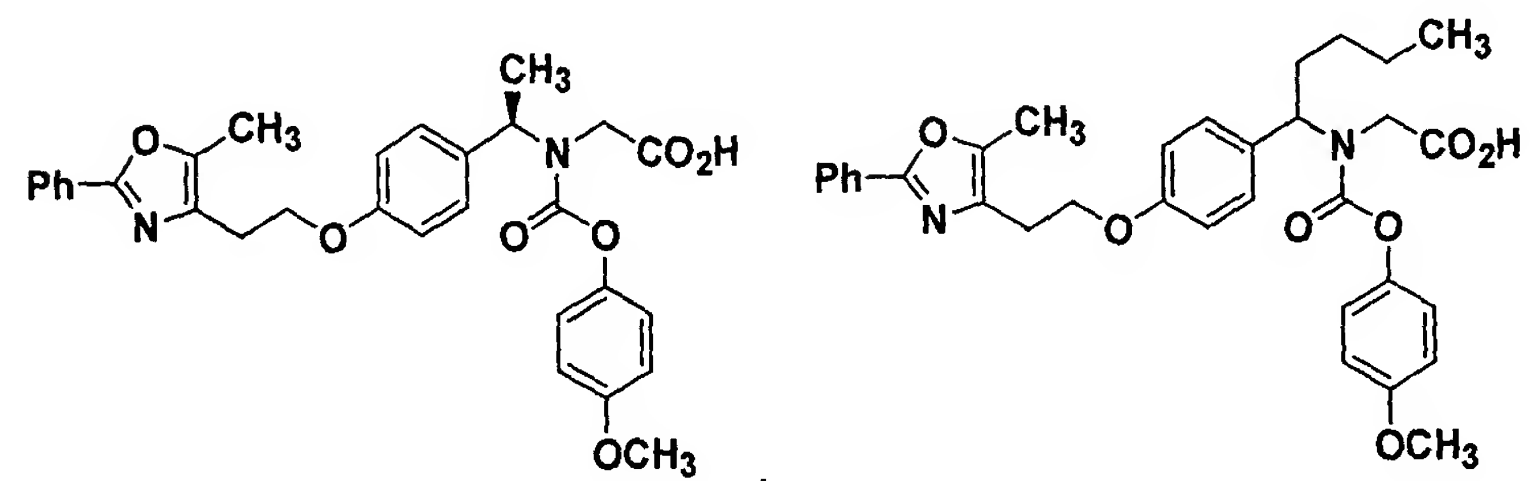
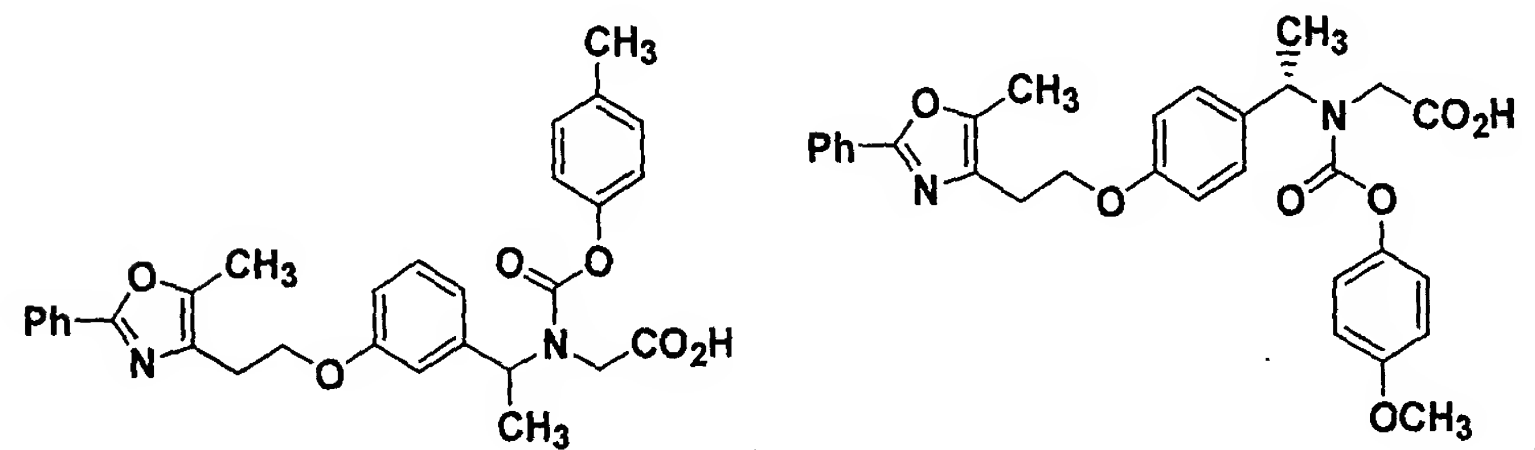
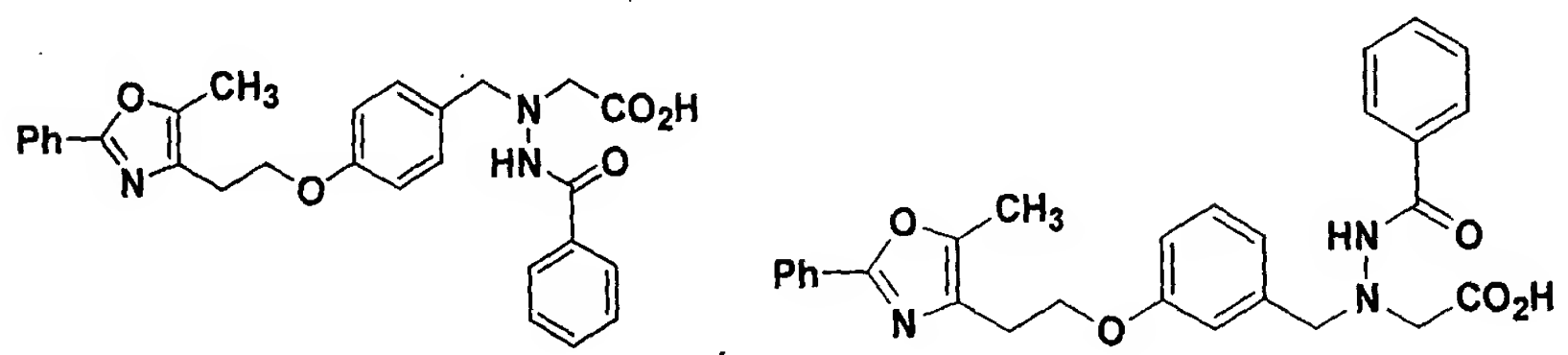
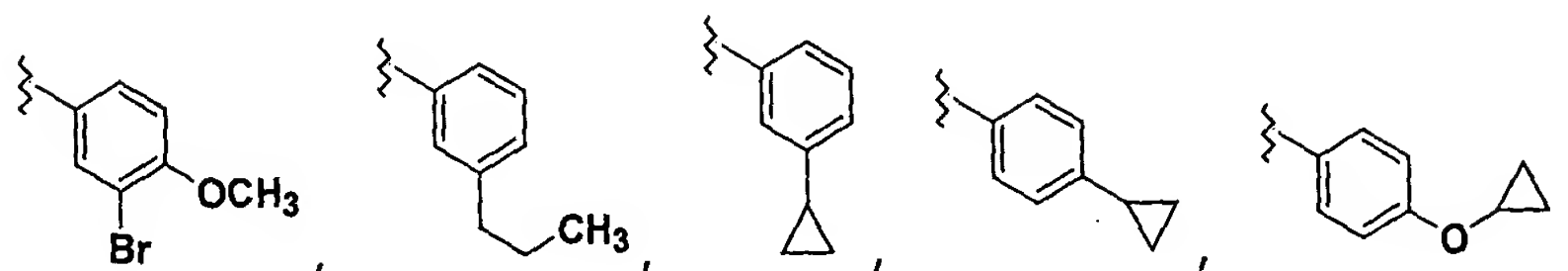
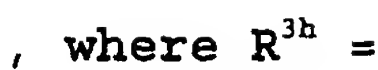


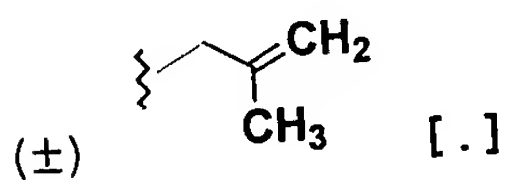
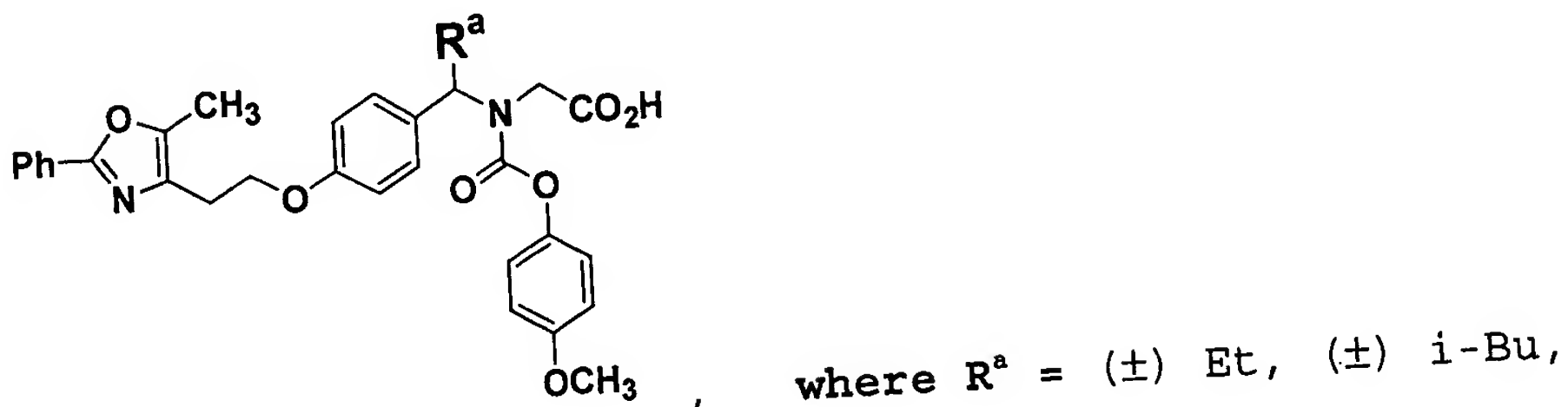
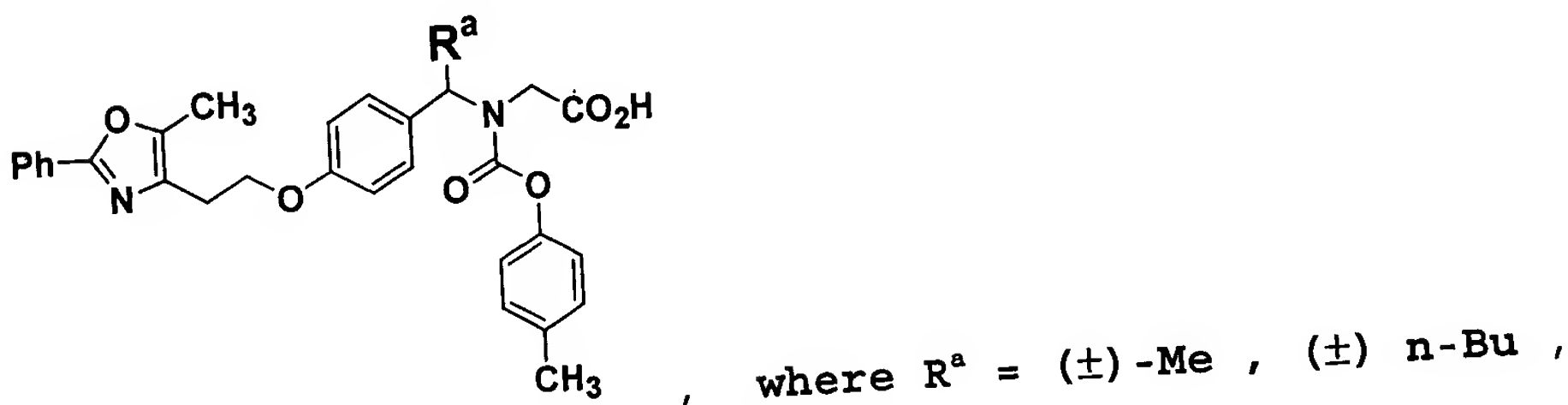
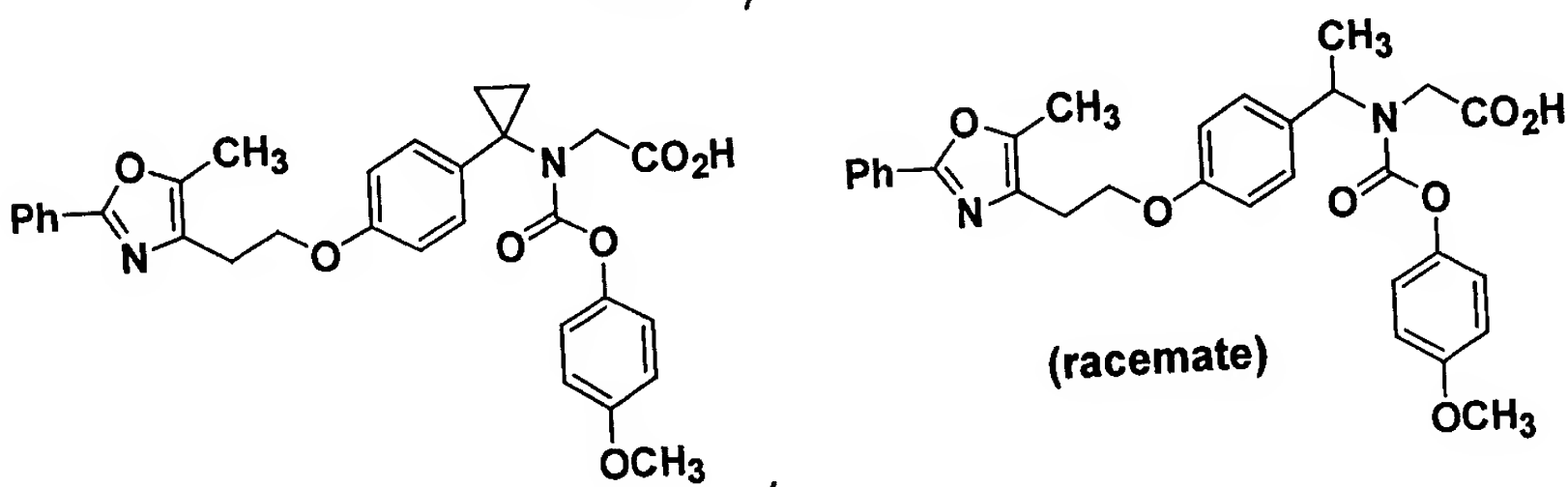
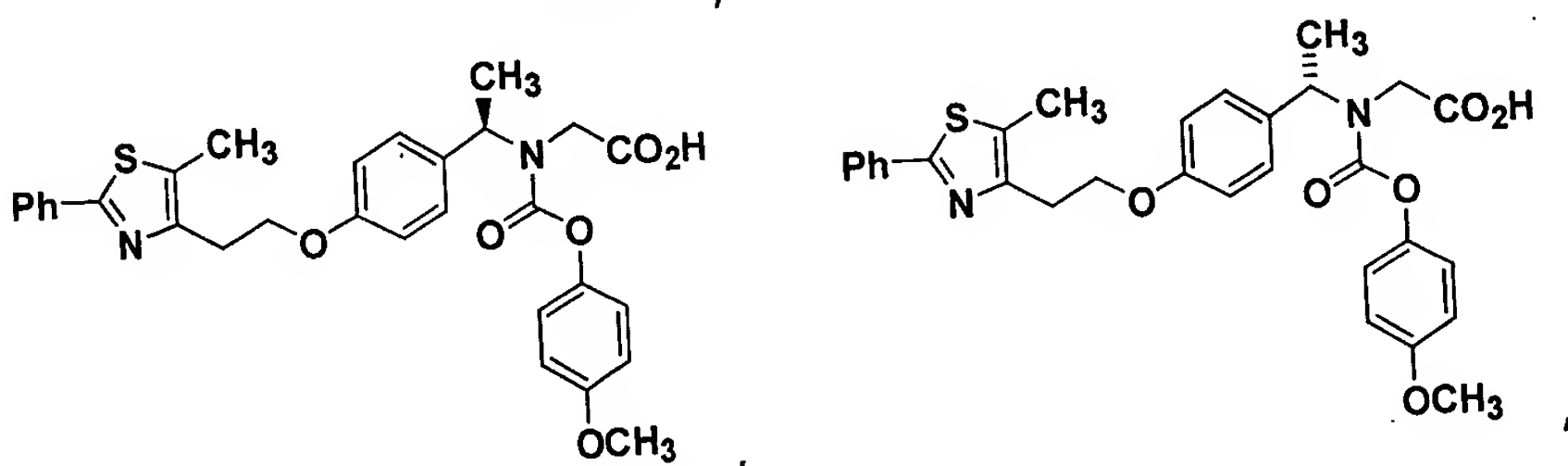
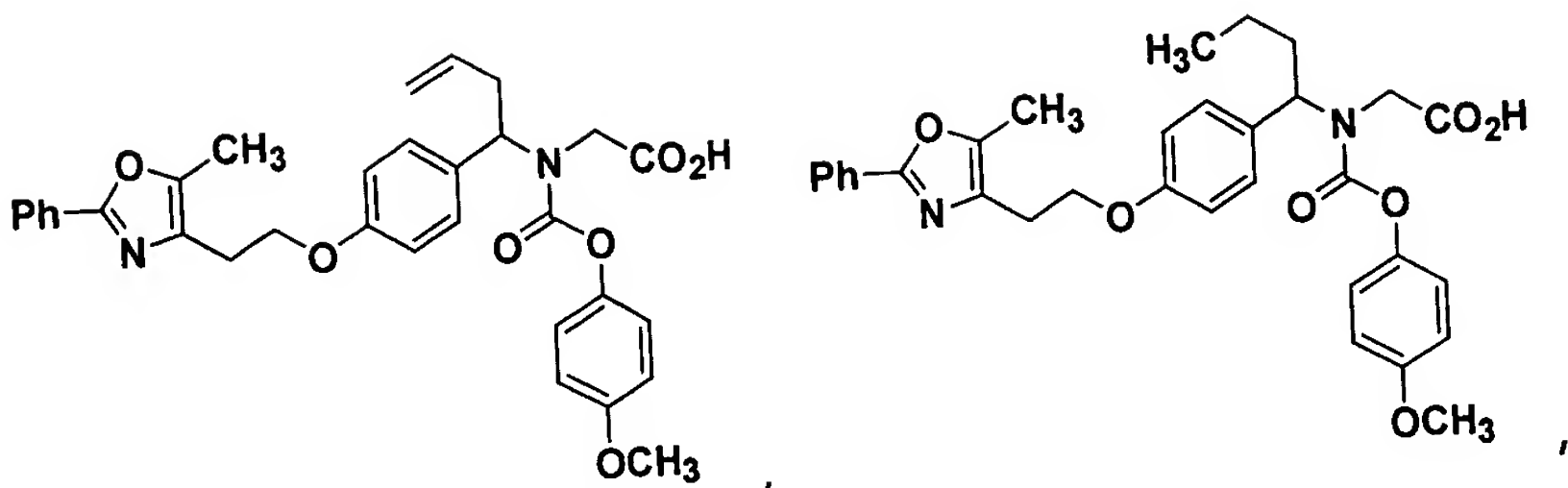
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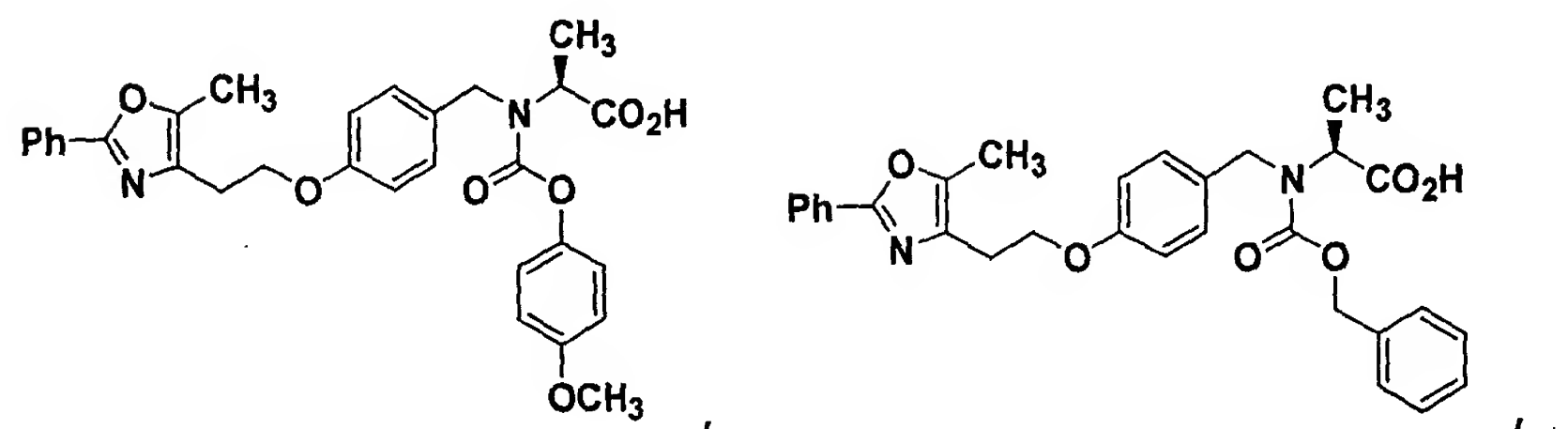
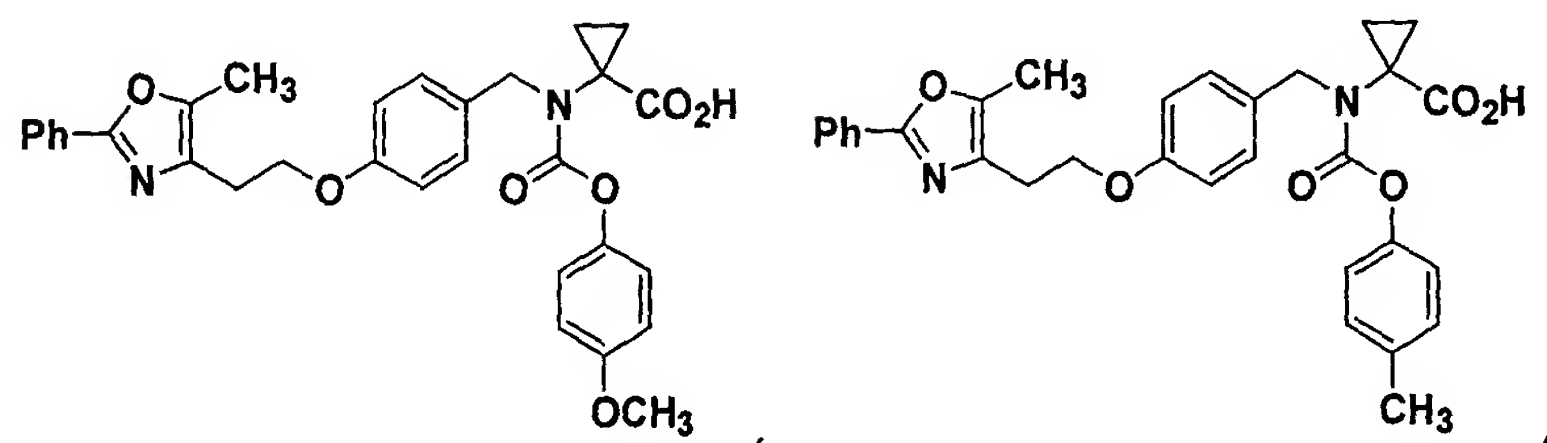
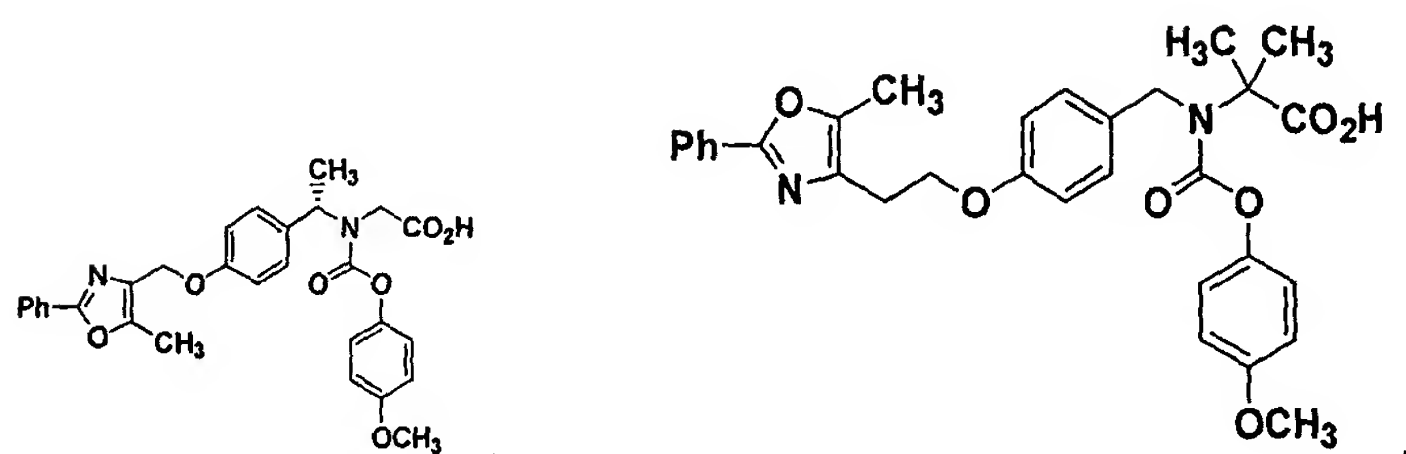
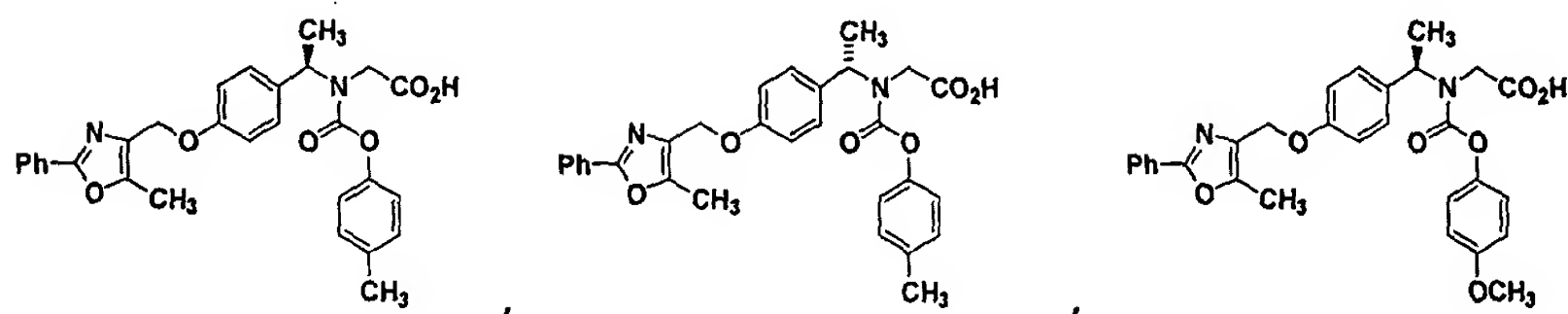
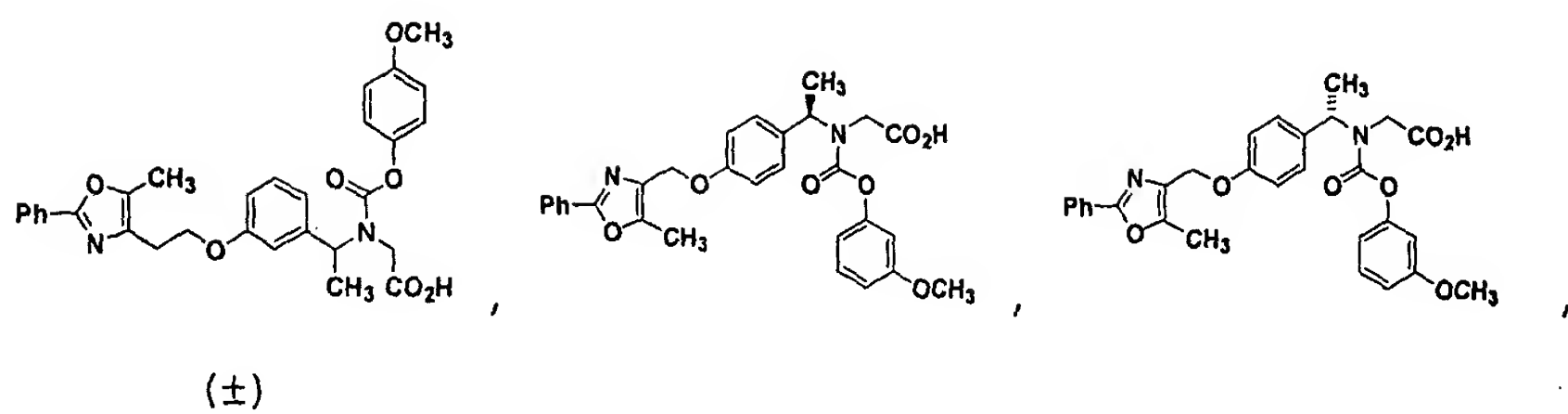


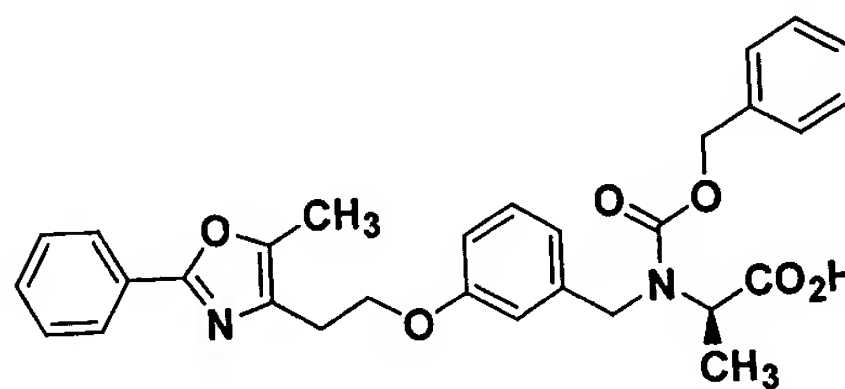
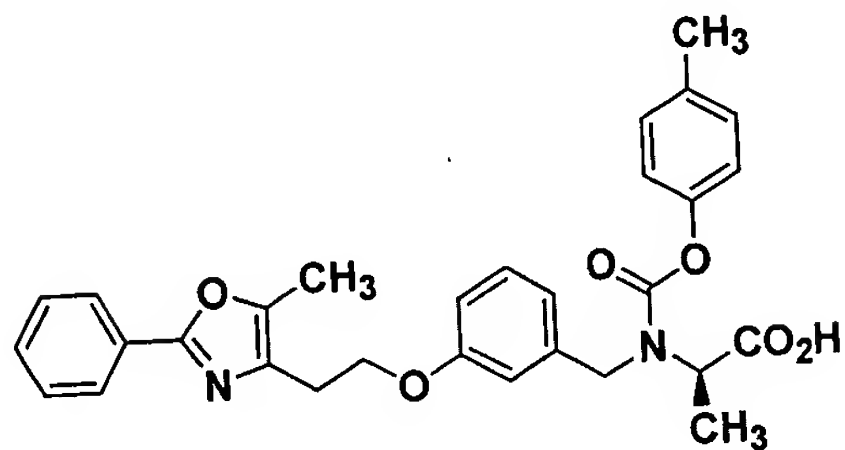
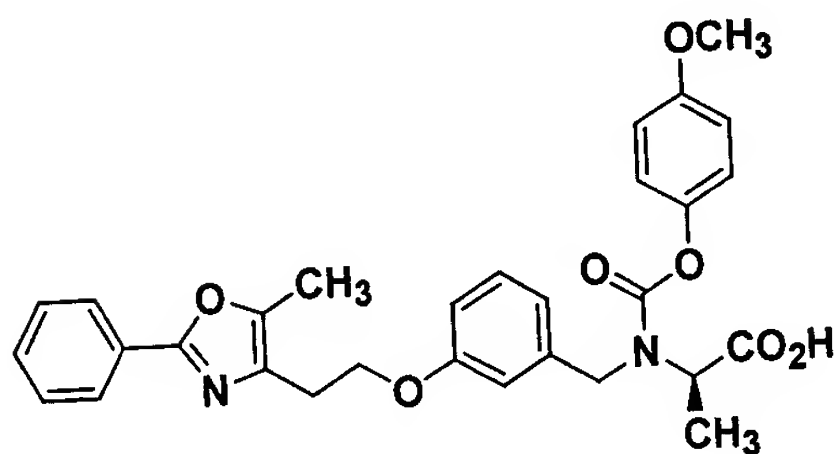
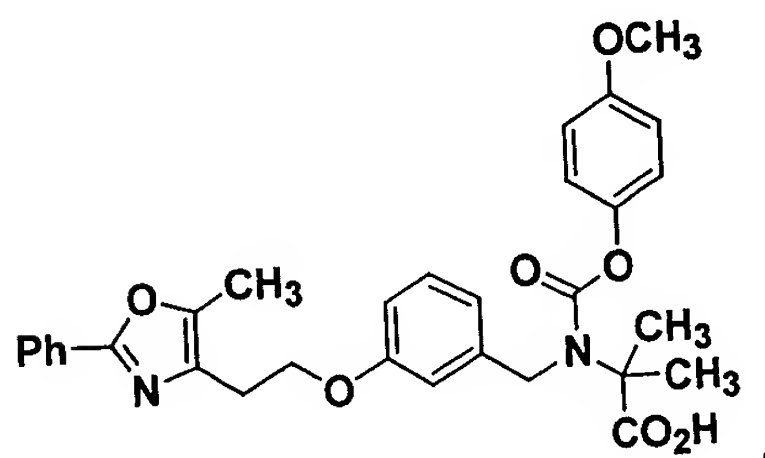
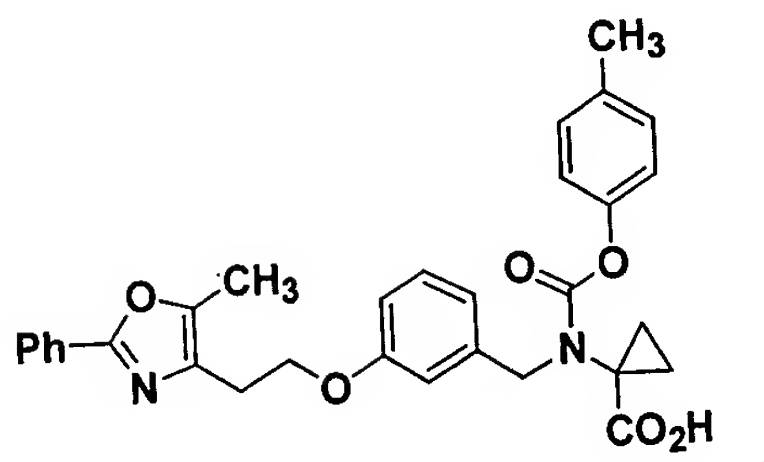
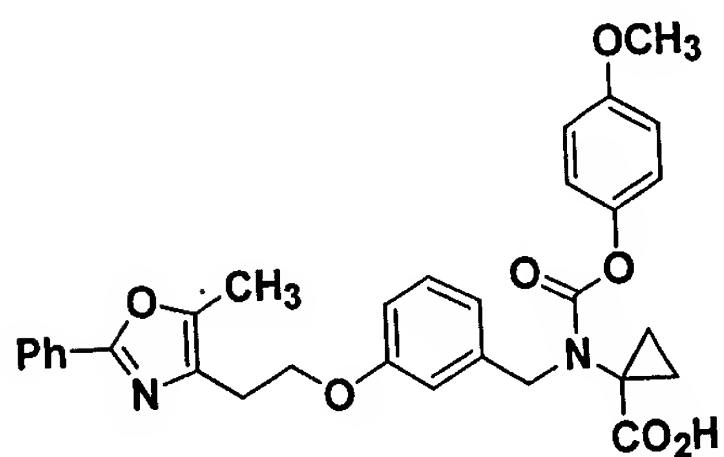
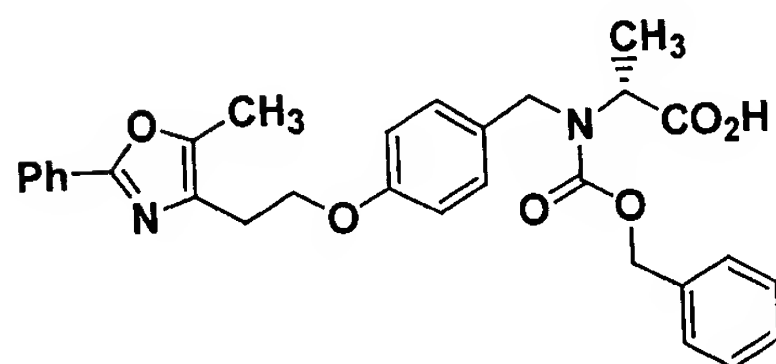
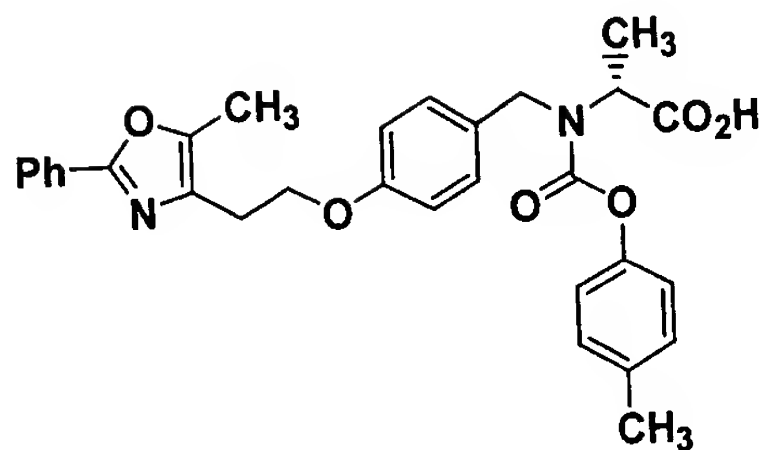
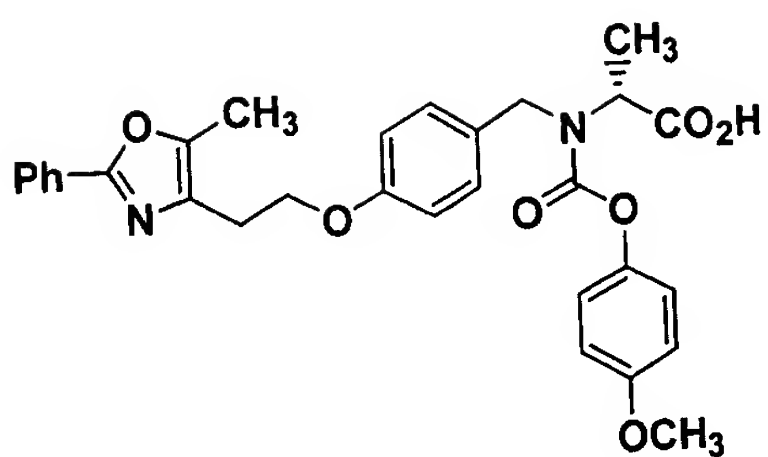
, where  $R^{3h} =$



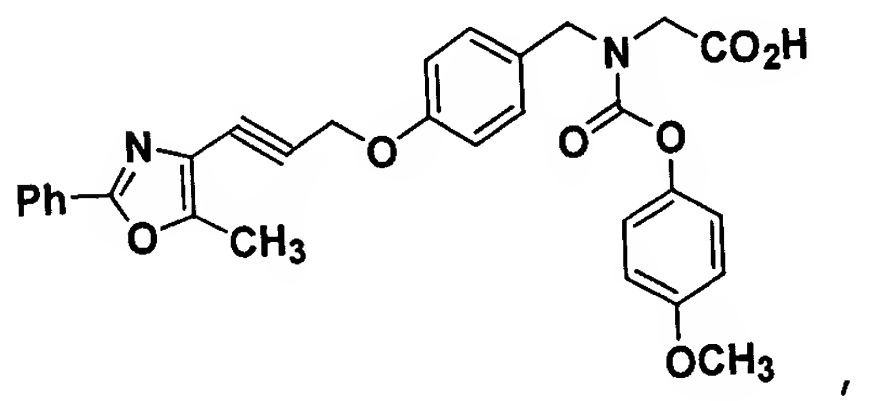
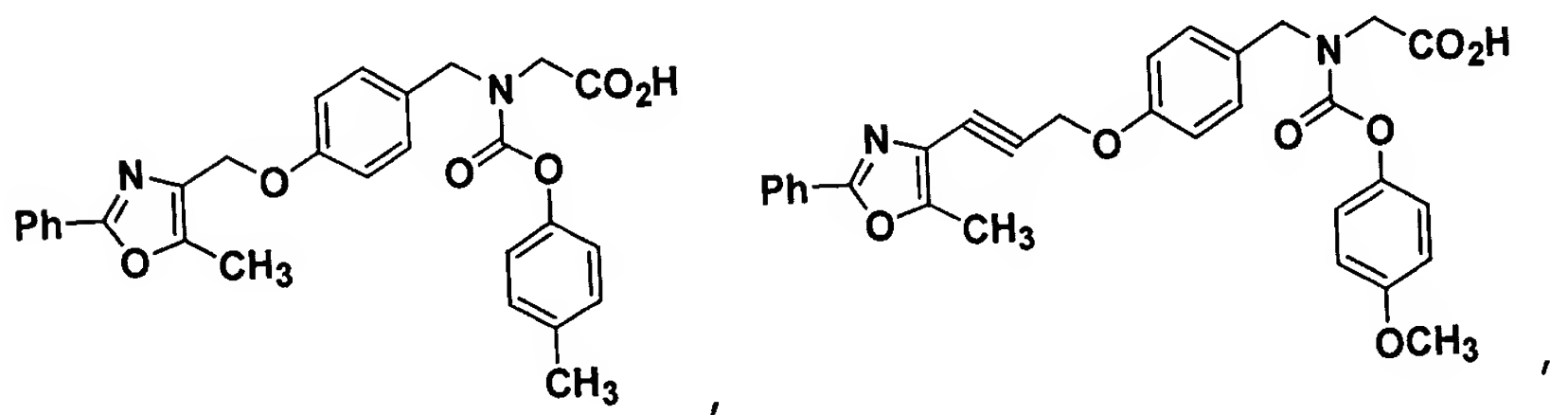
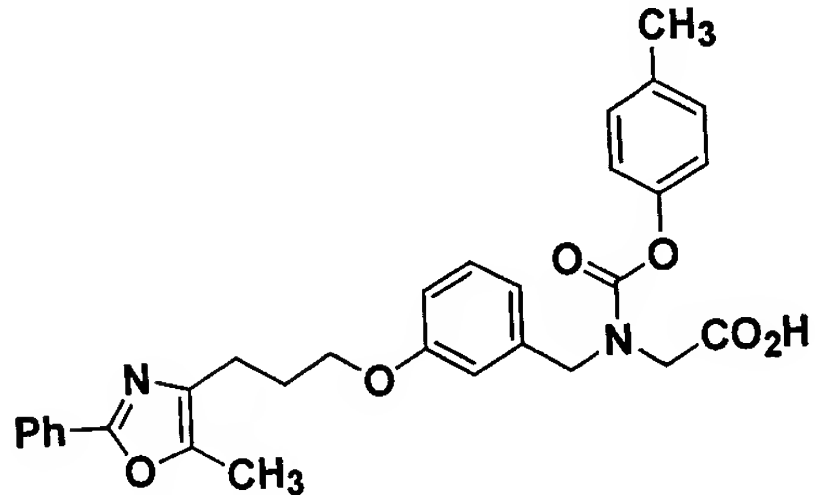
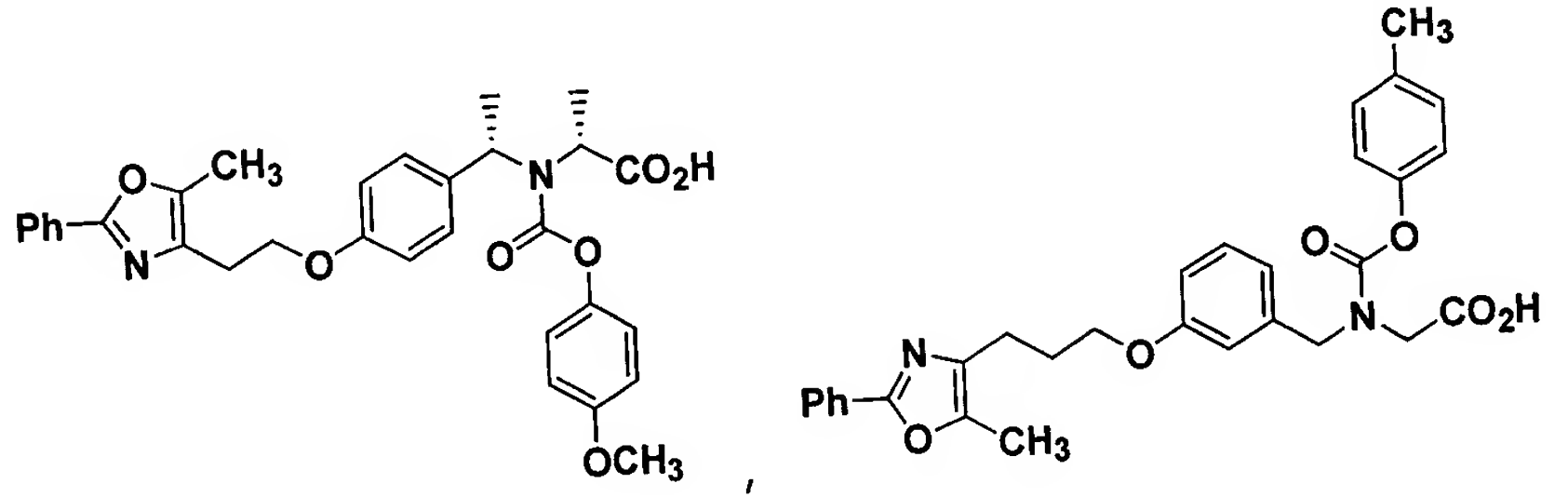
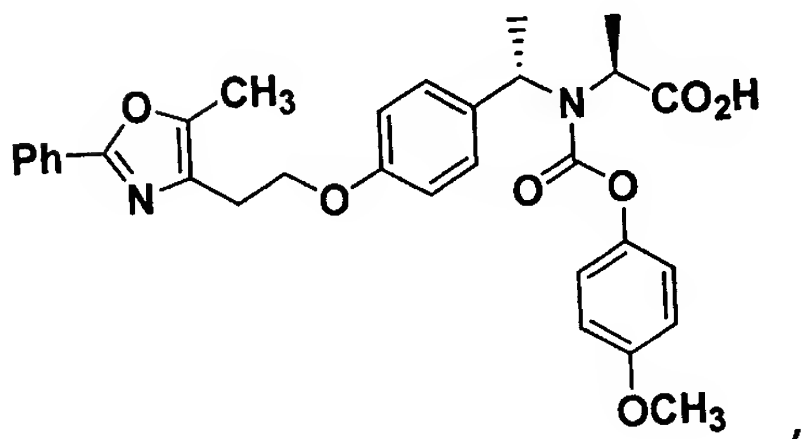
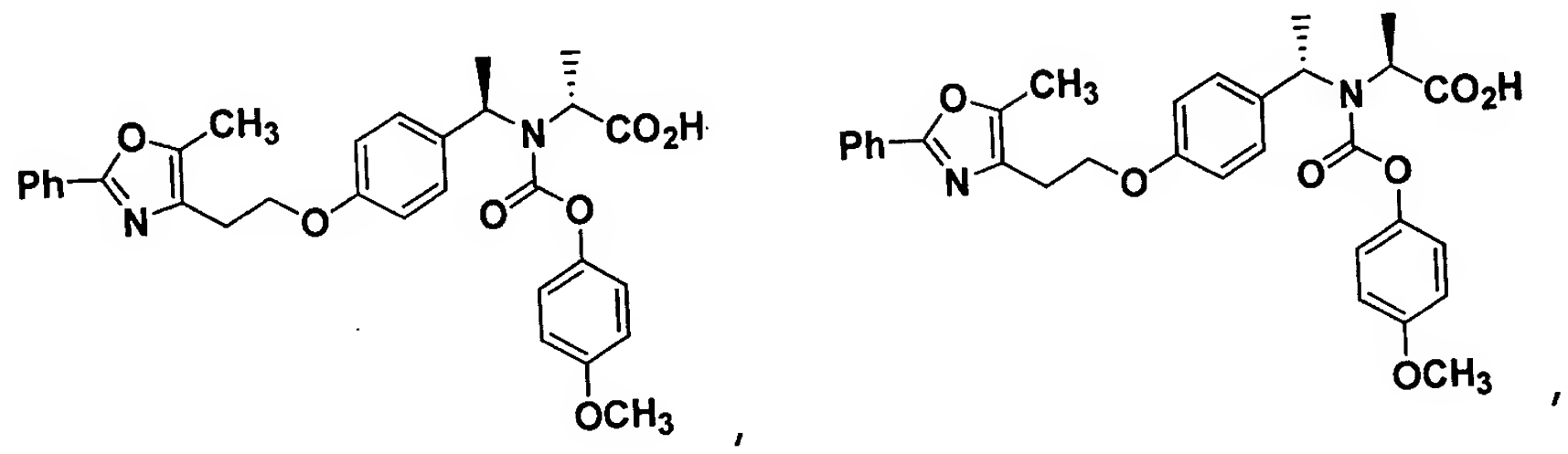
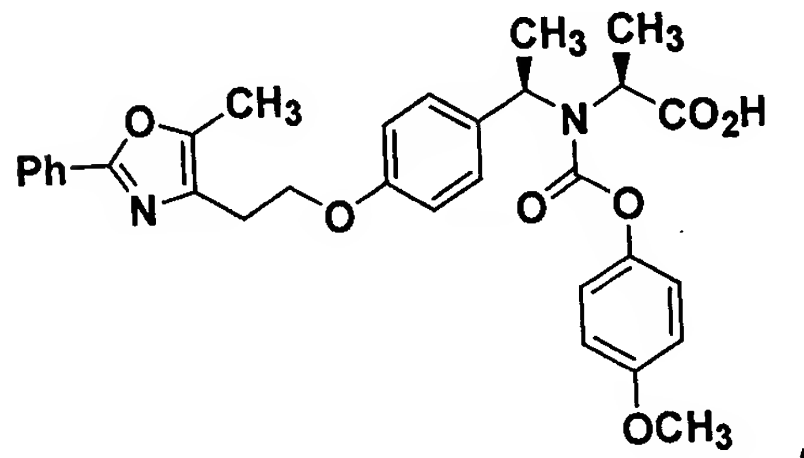
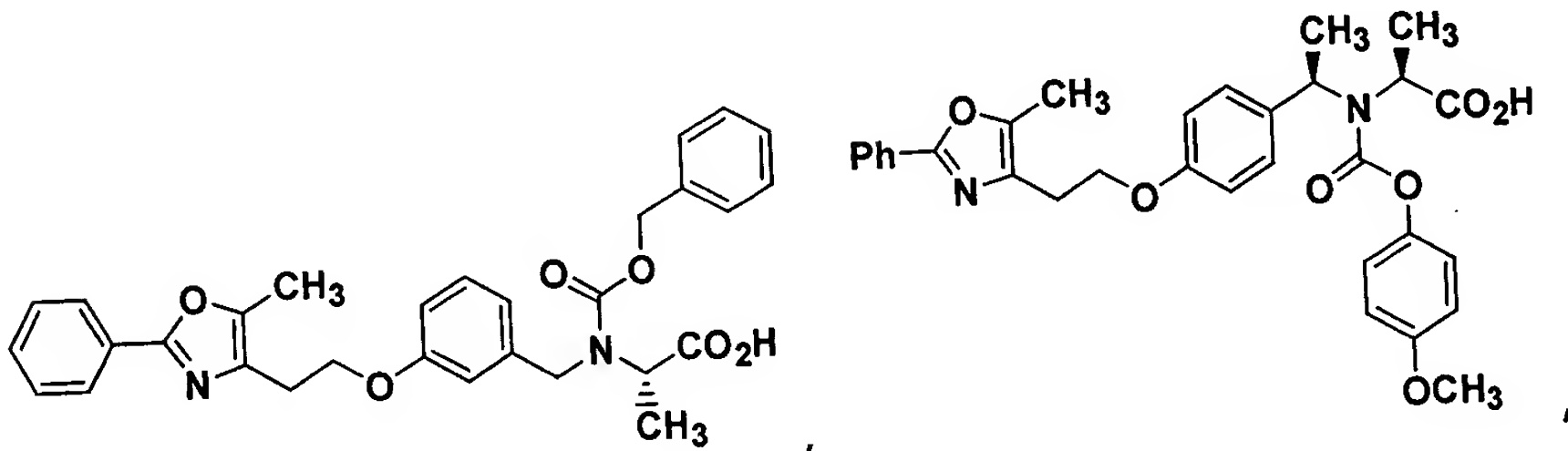
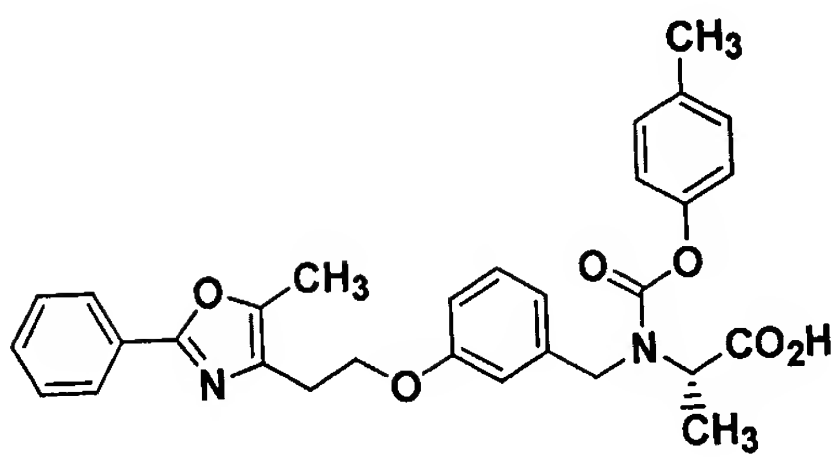
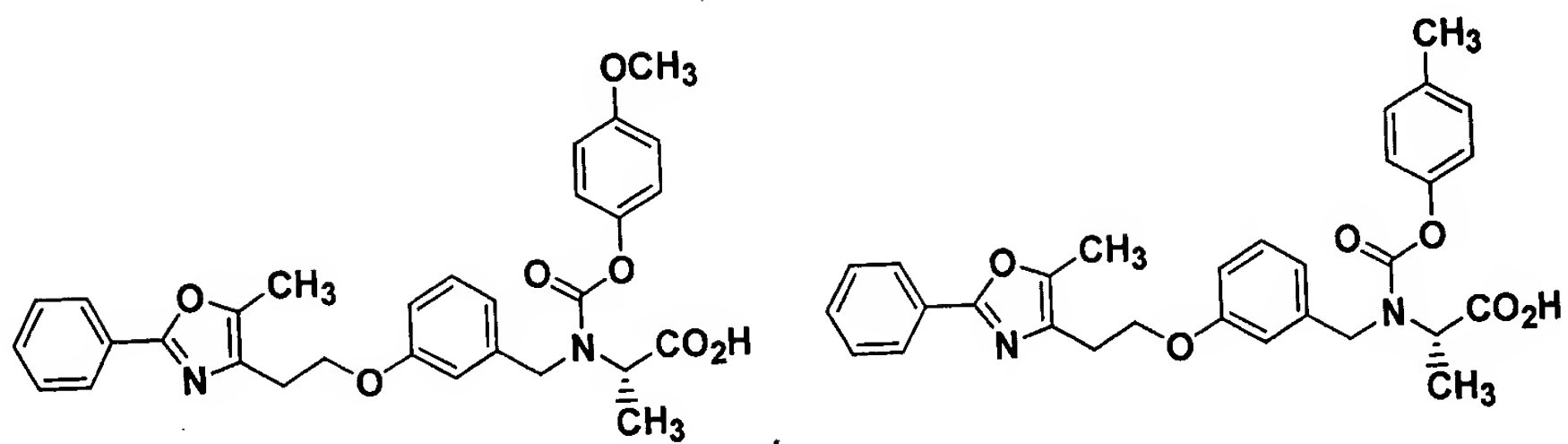


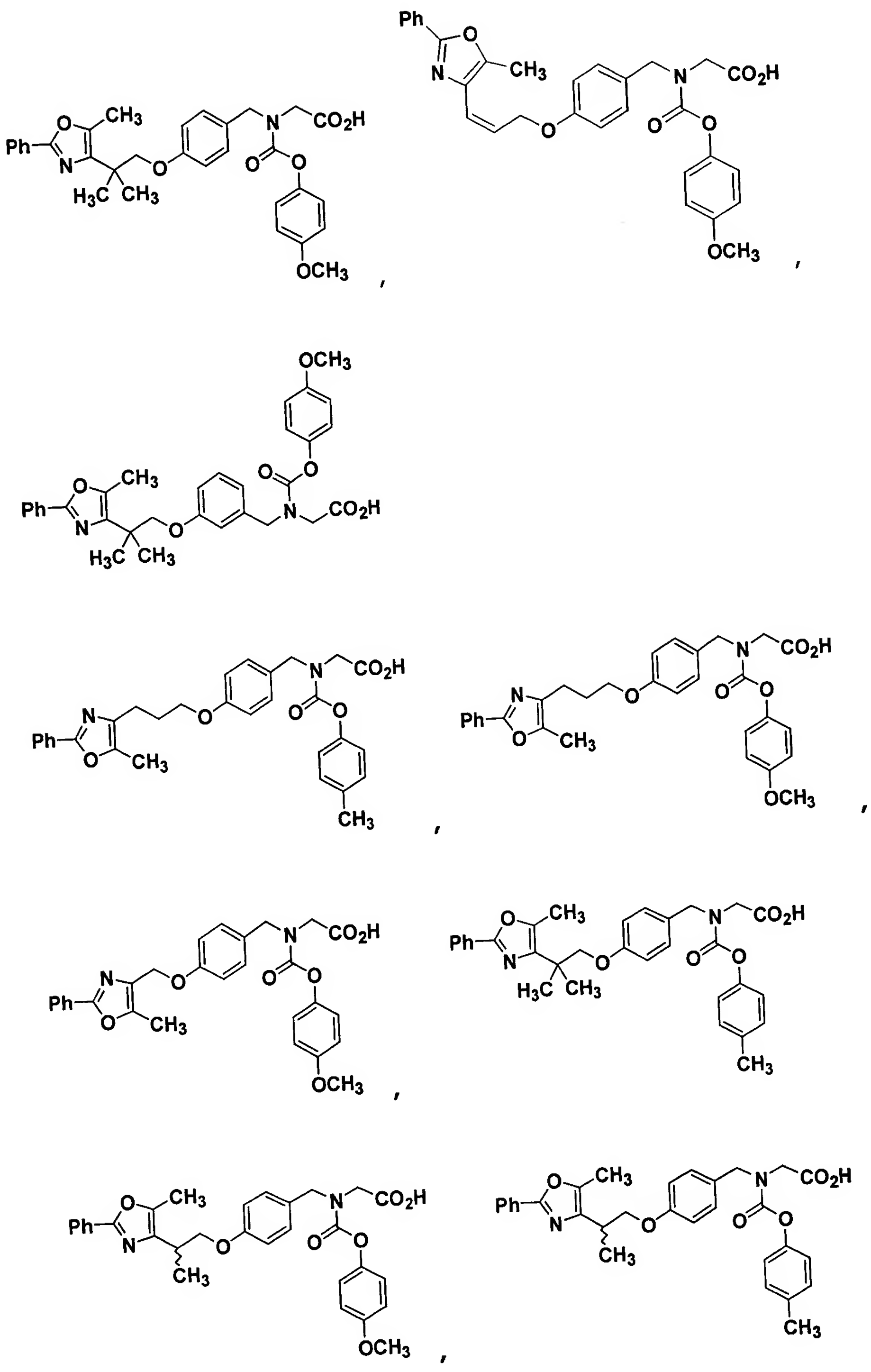


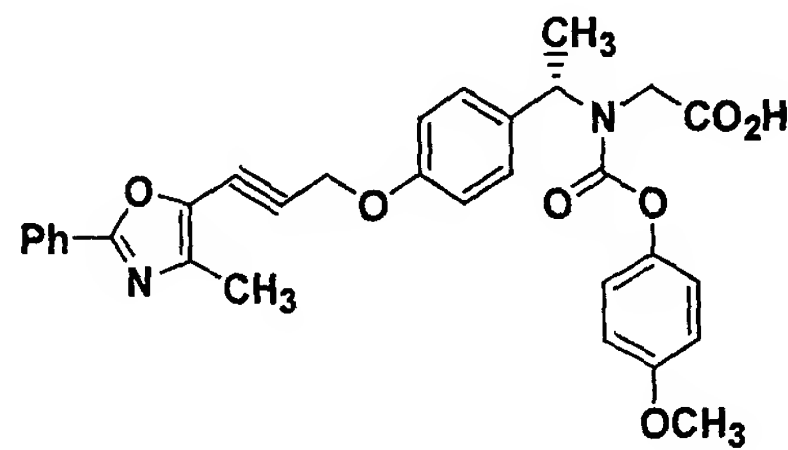
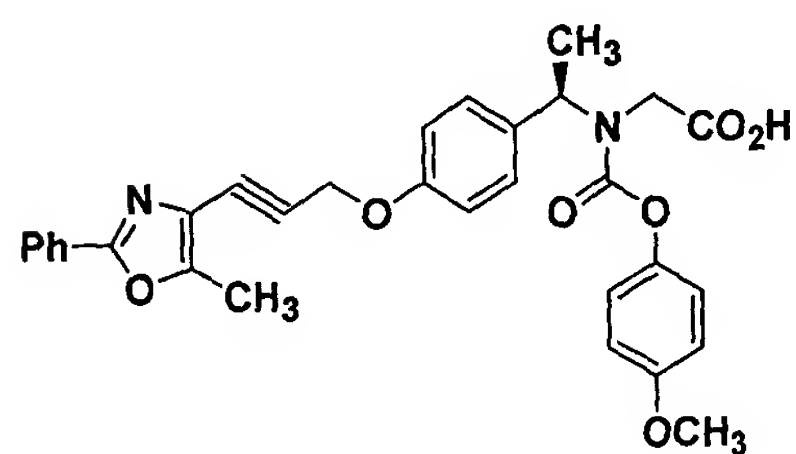
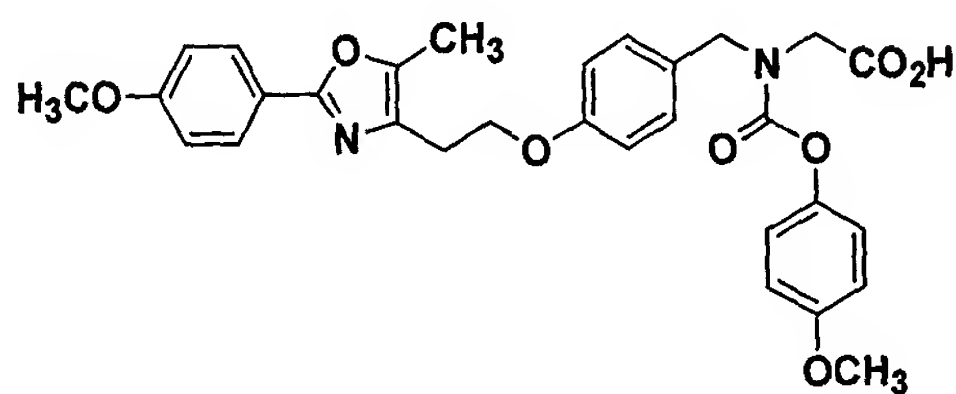
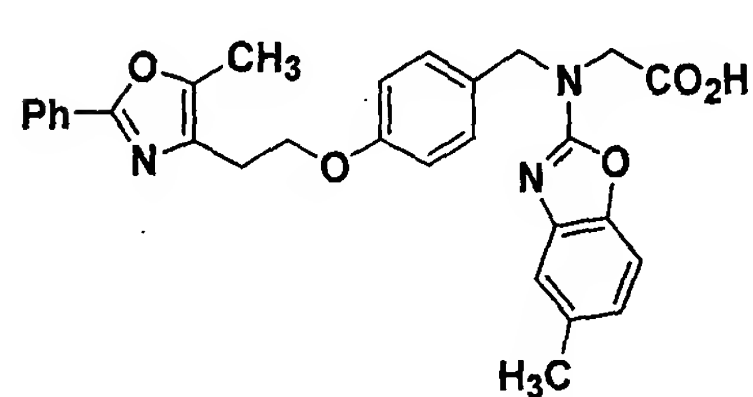
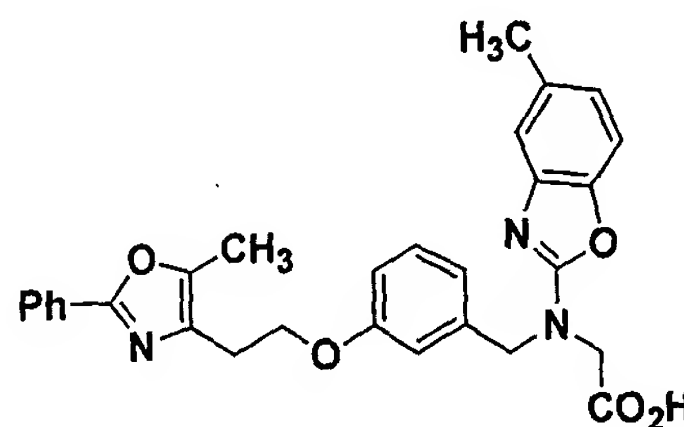
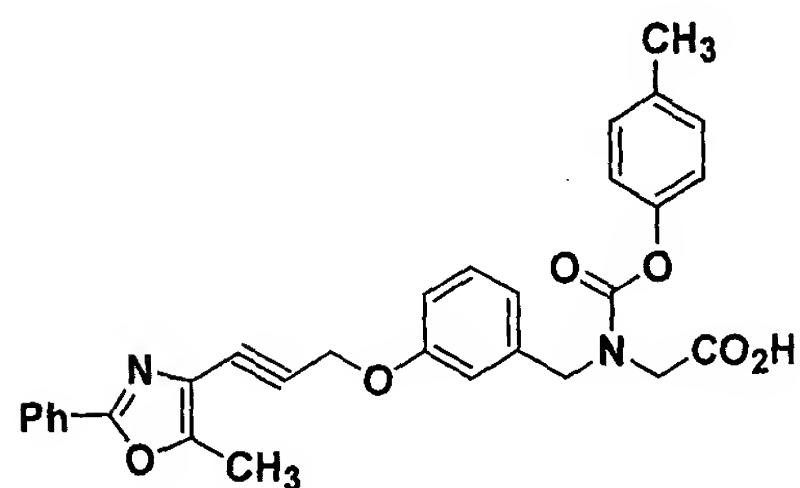
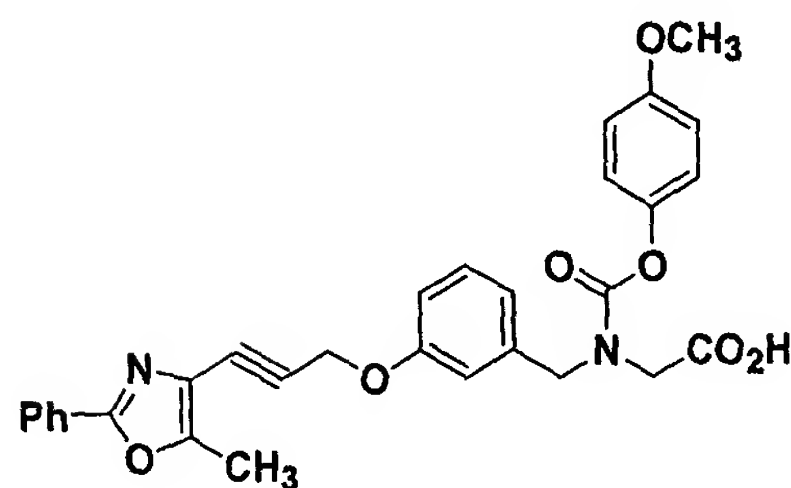
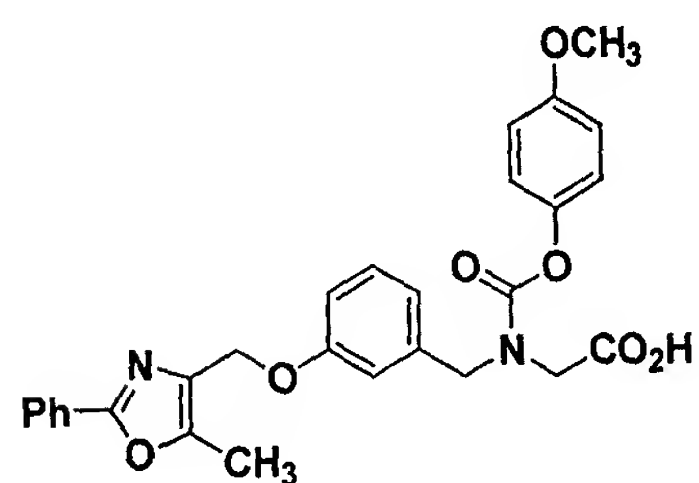
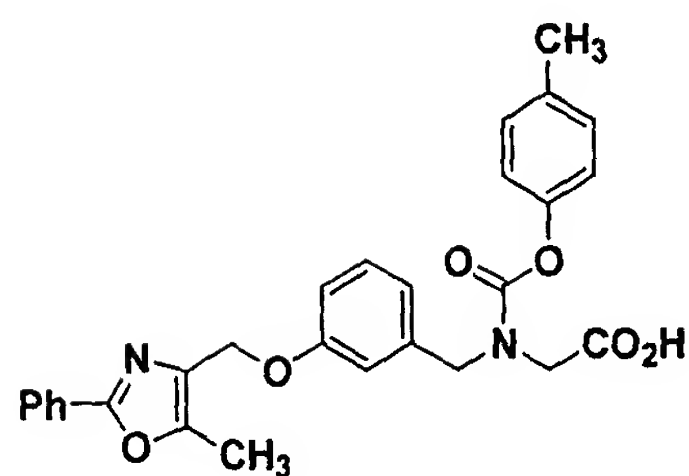
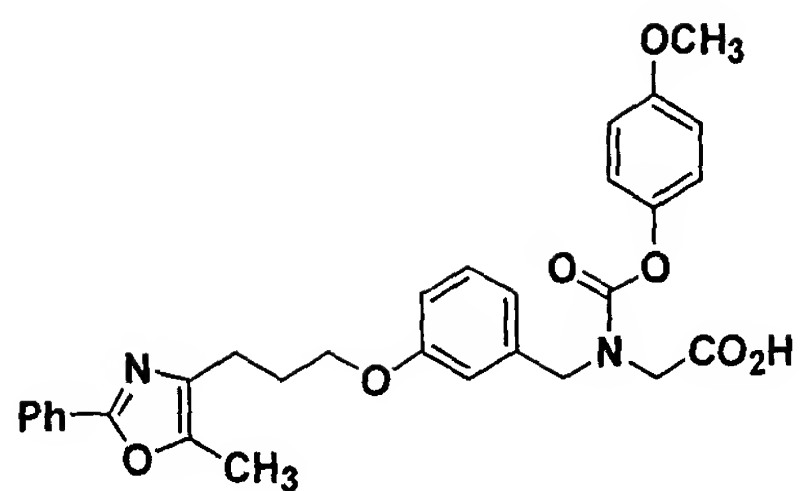




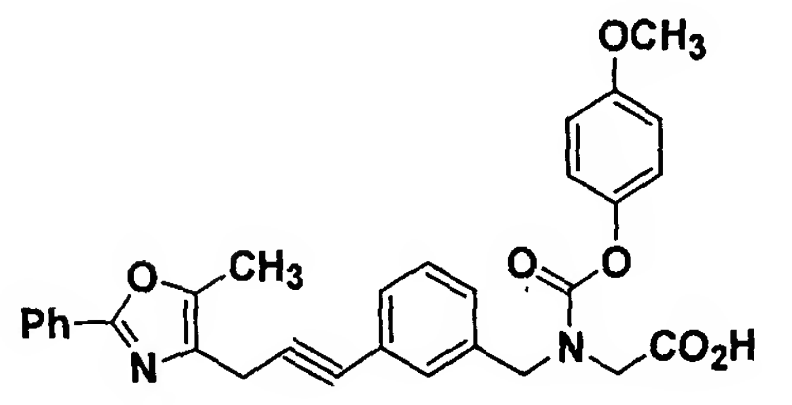
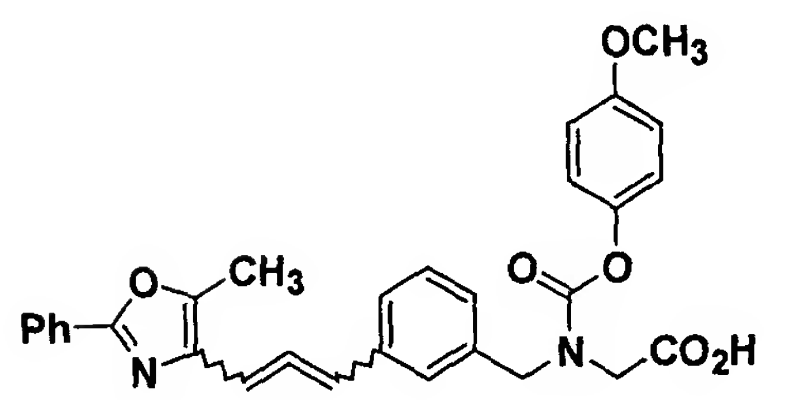
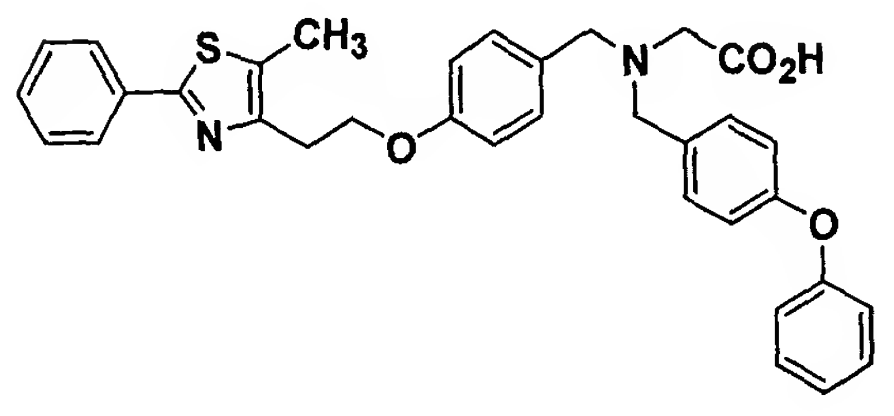
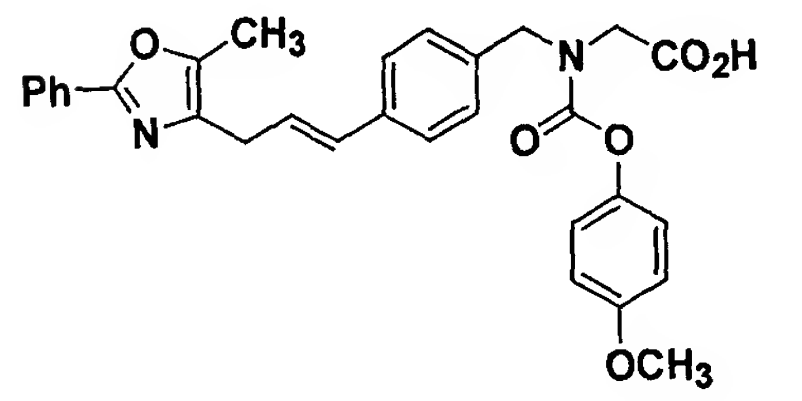
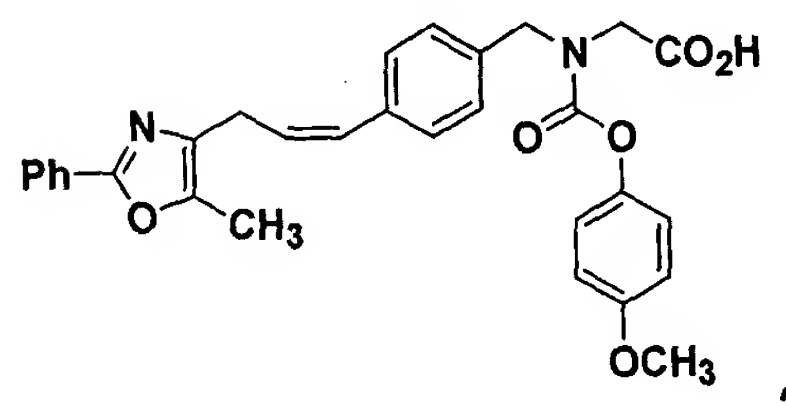
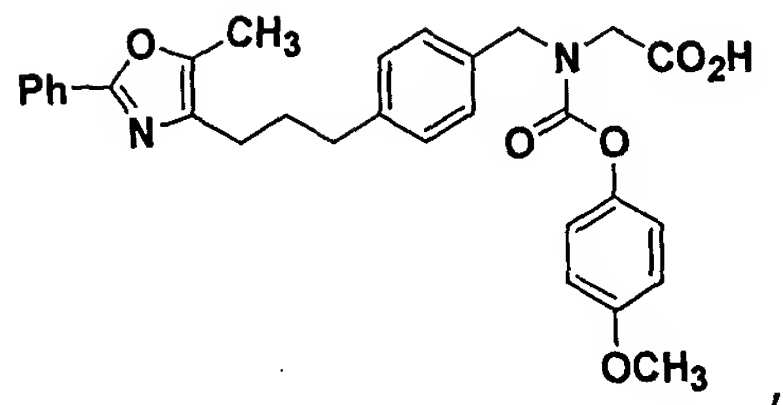
ASE LA29a DIV-2

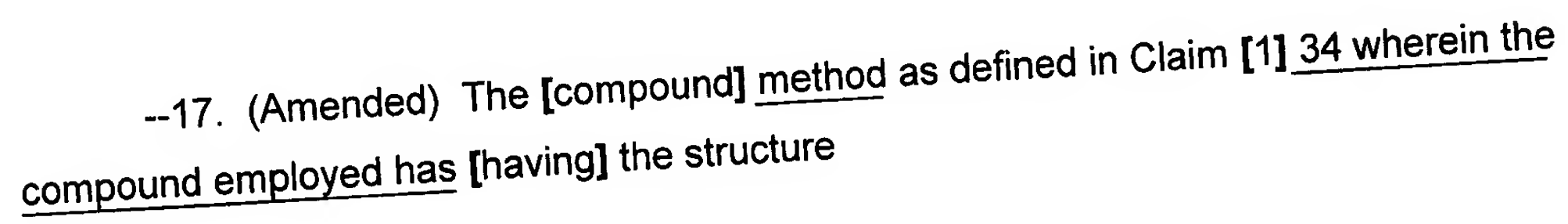


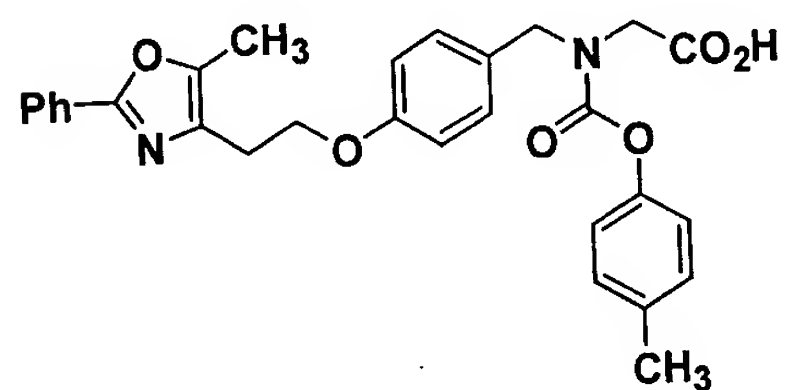
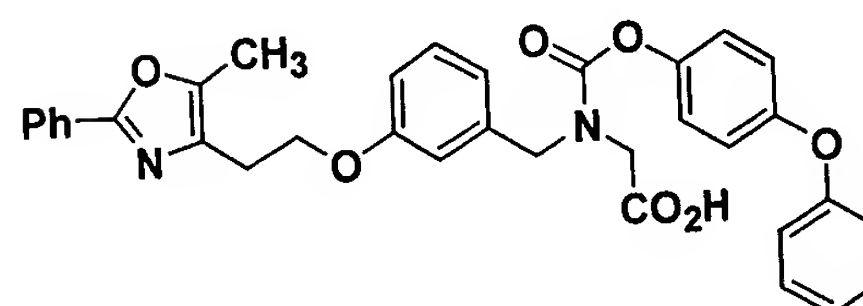
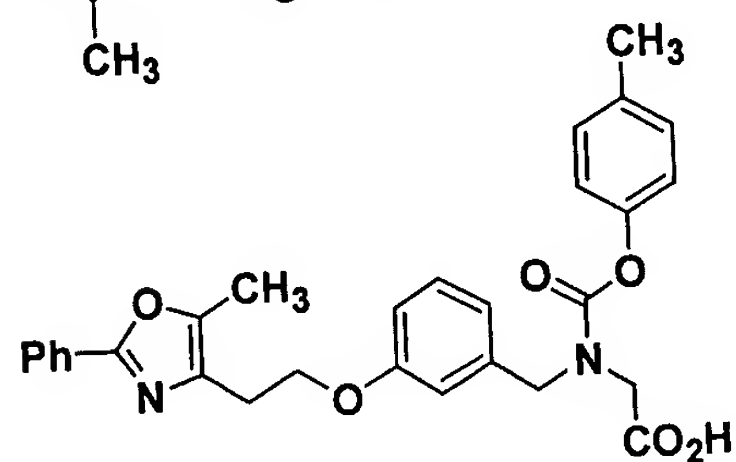
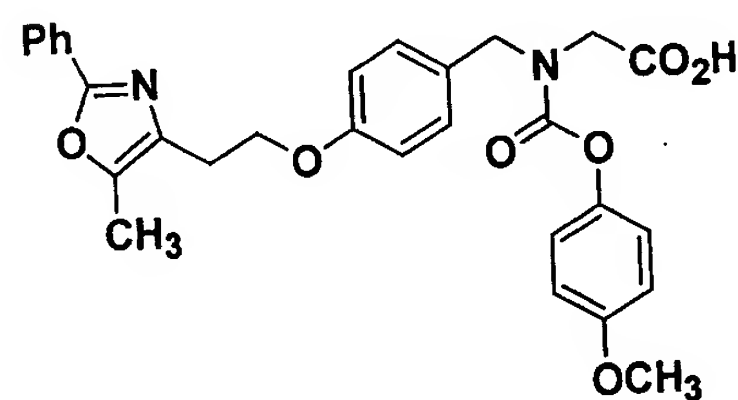
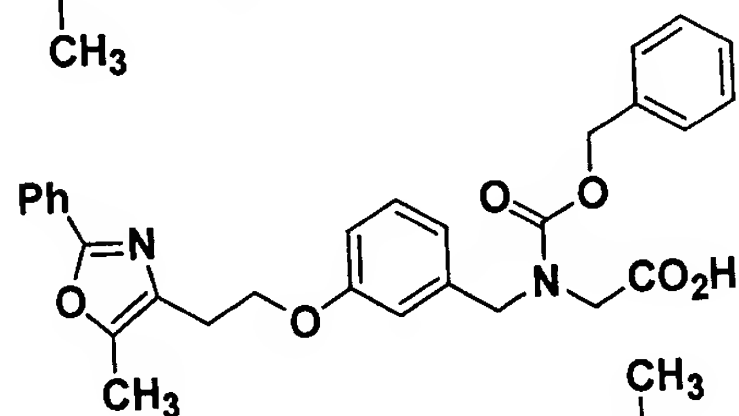
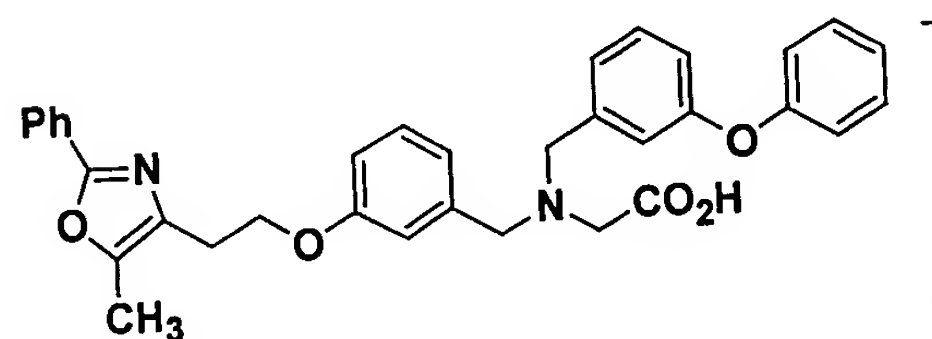
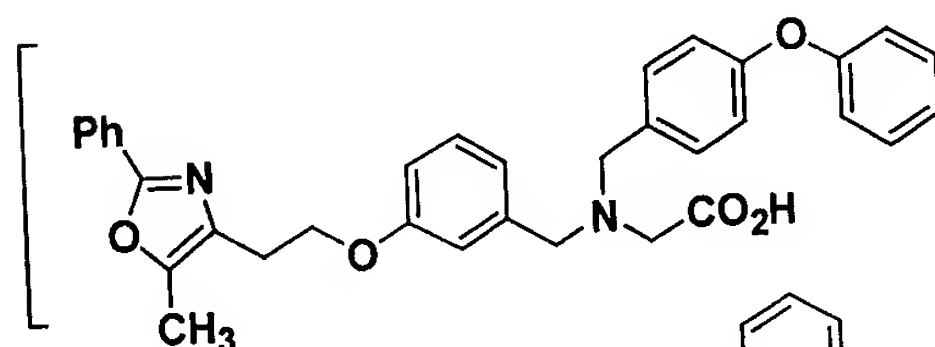
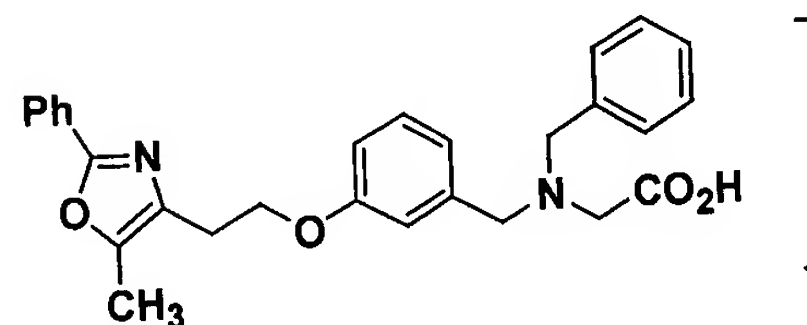
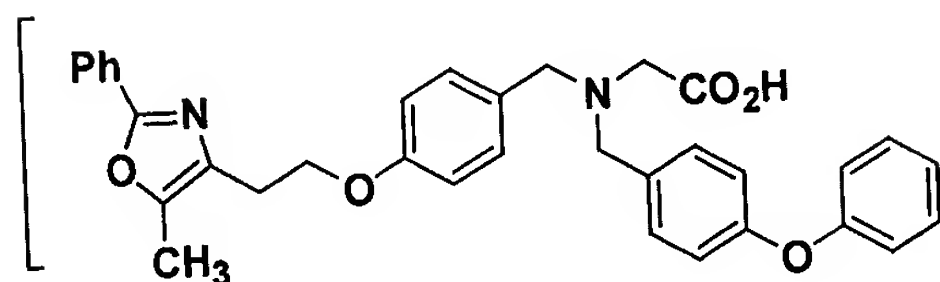
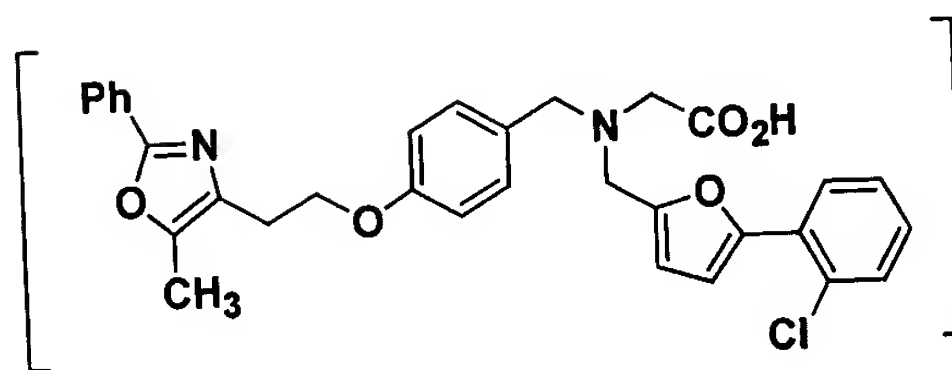
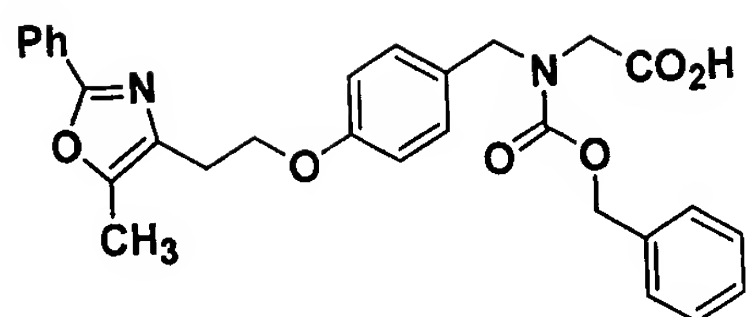


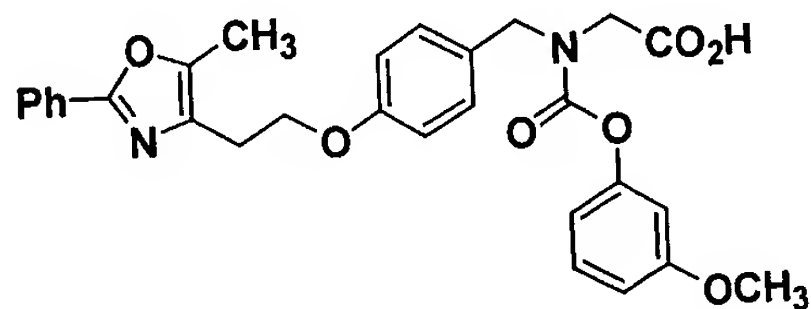
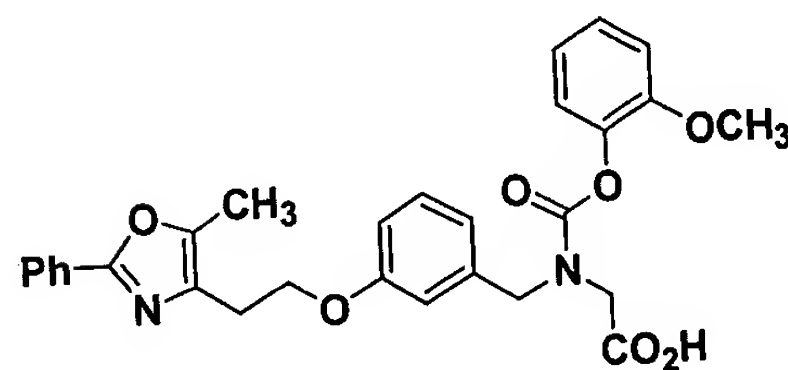
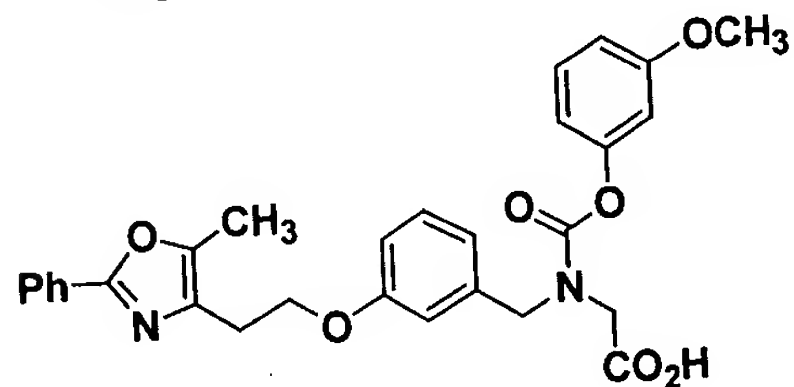
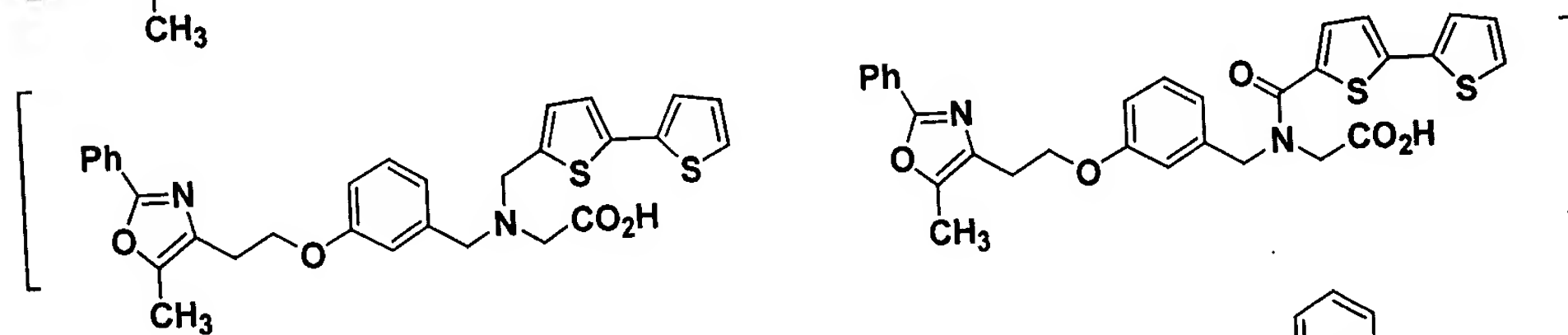
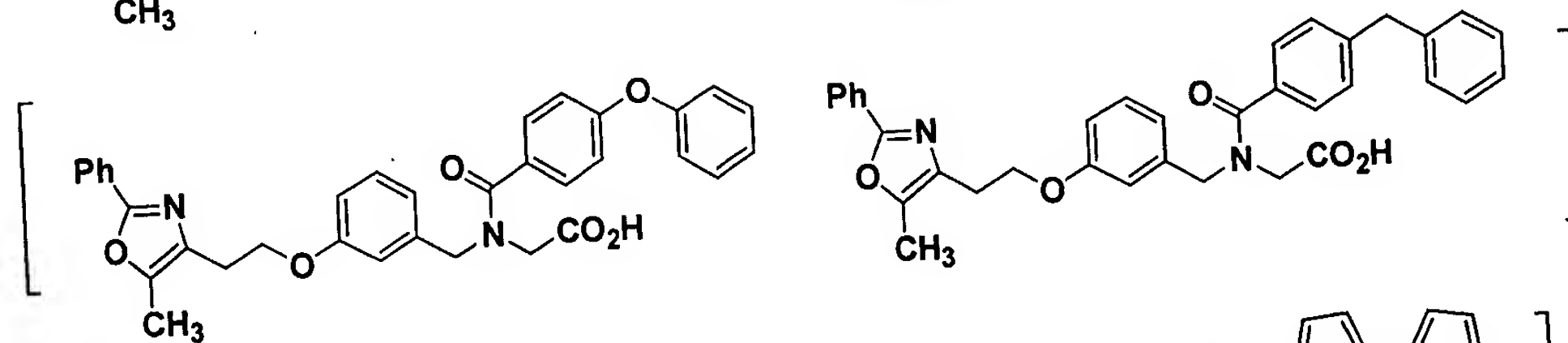
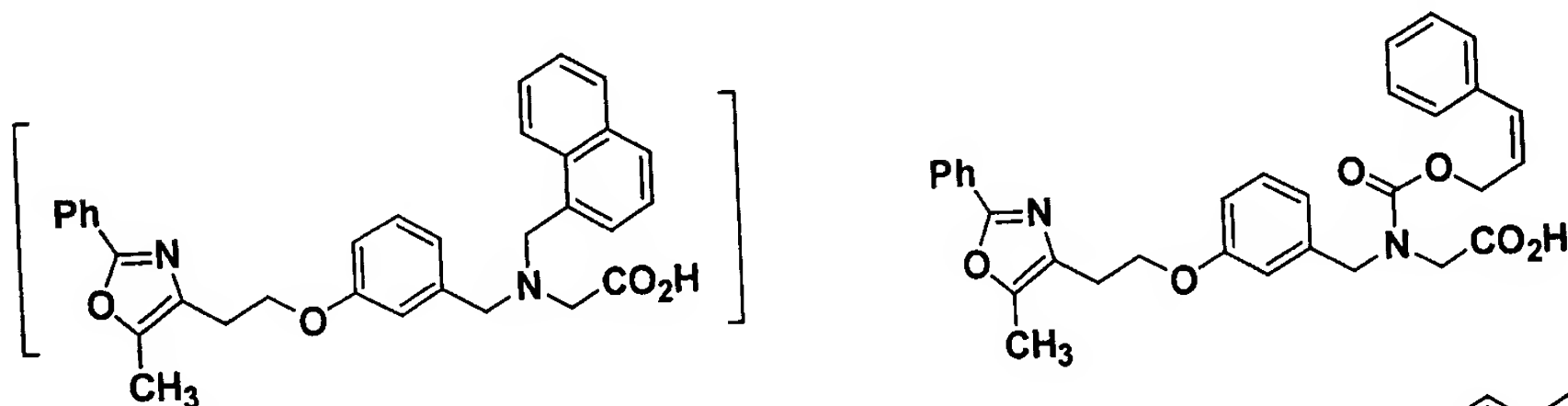
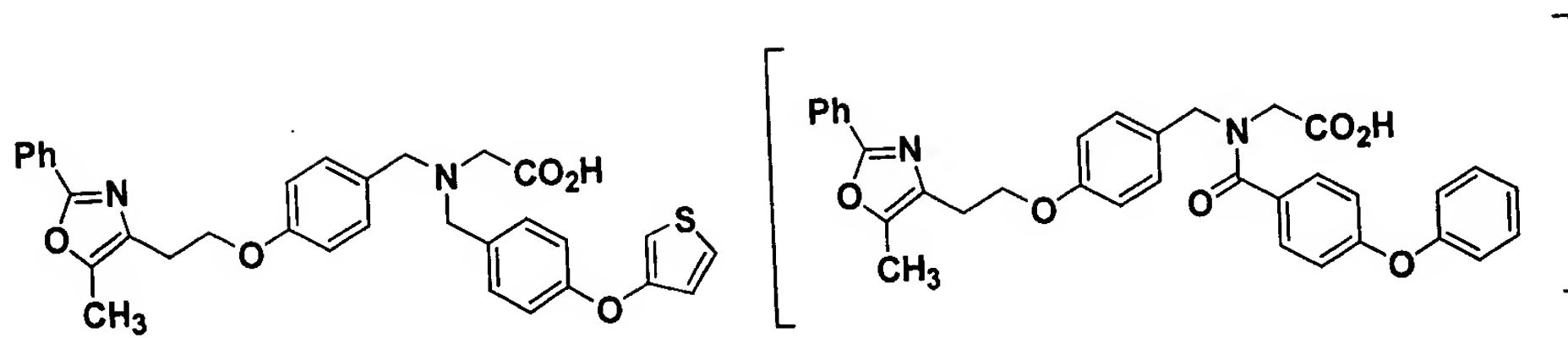


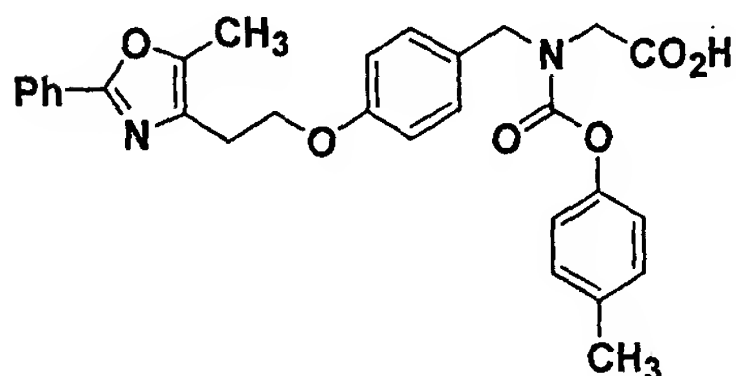
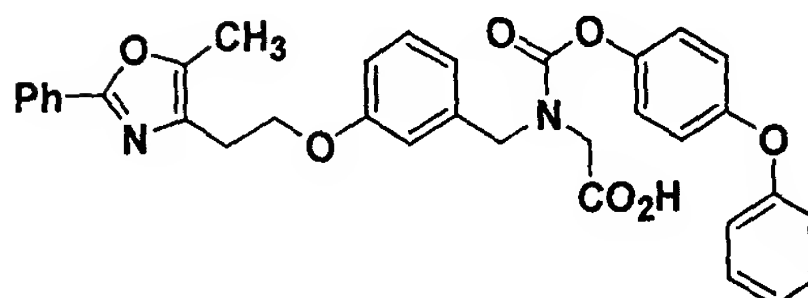
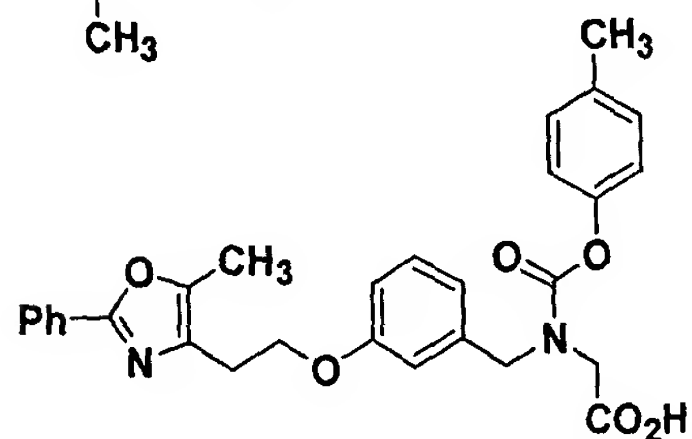
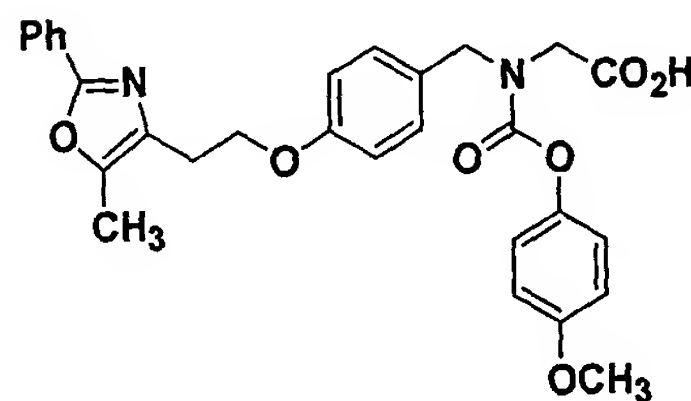
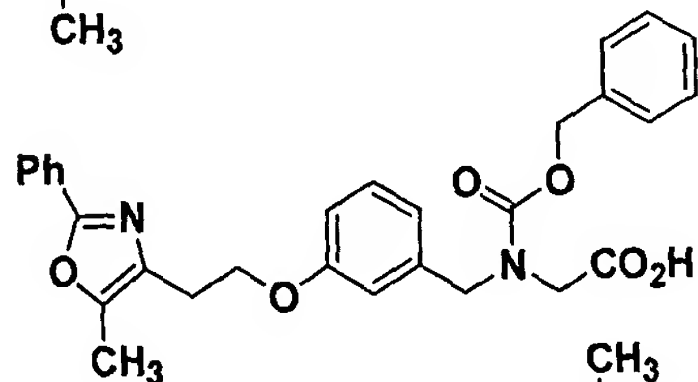
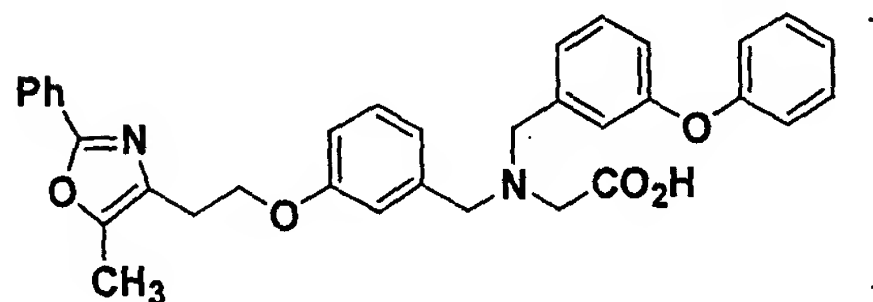
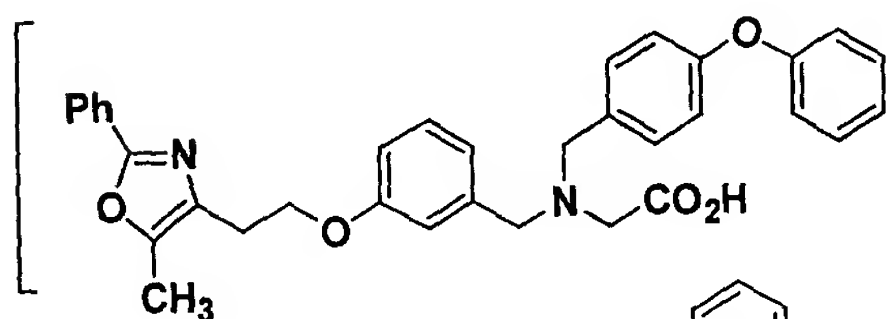
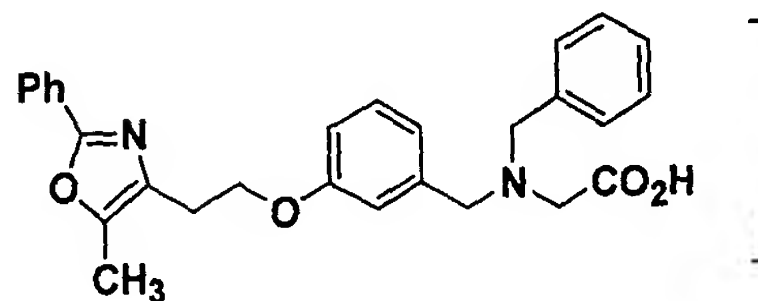
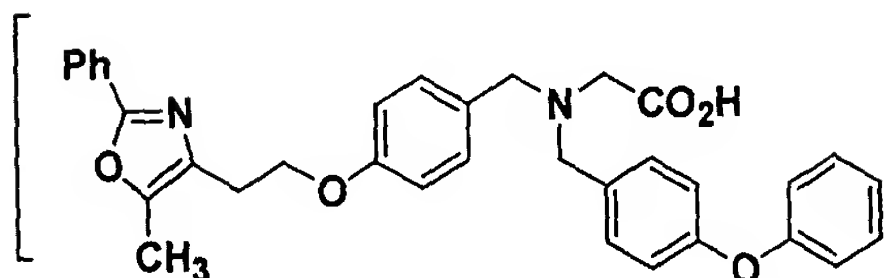
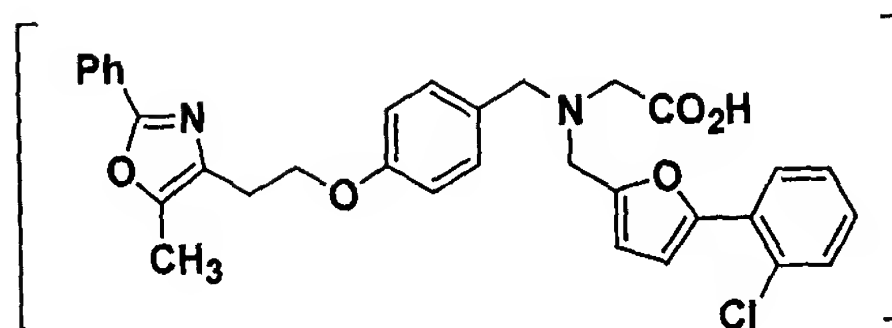
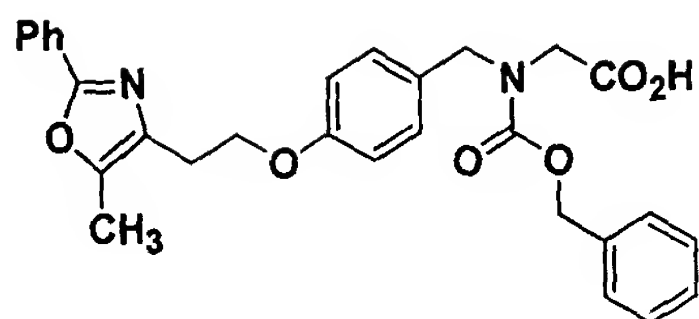




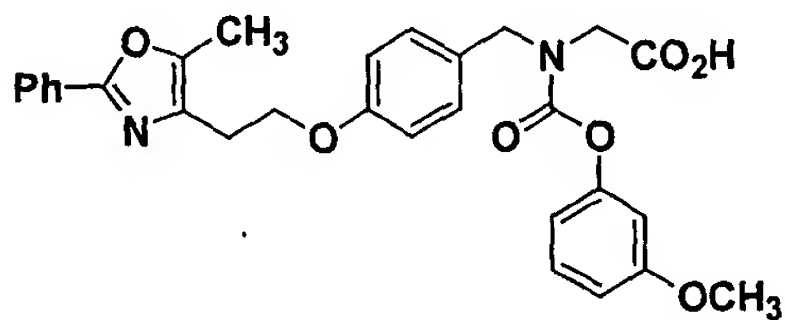
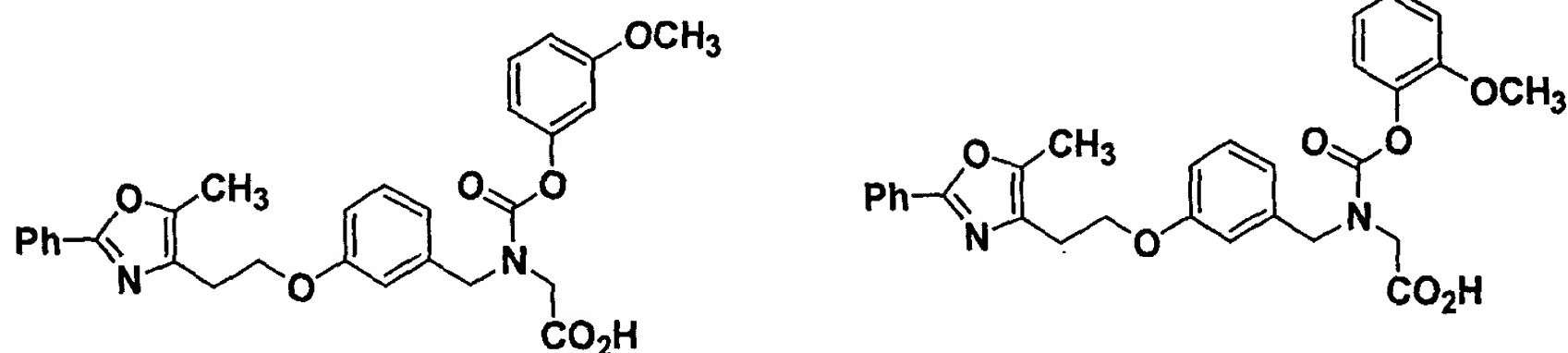
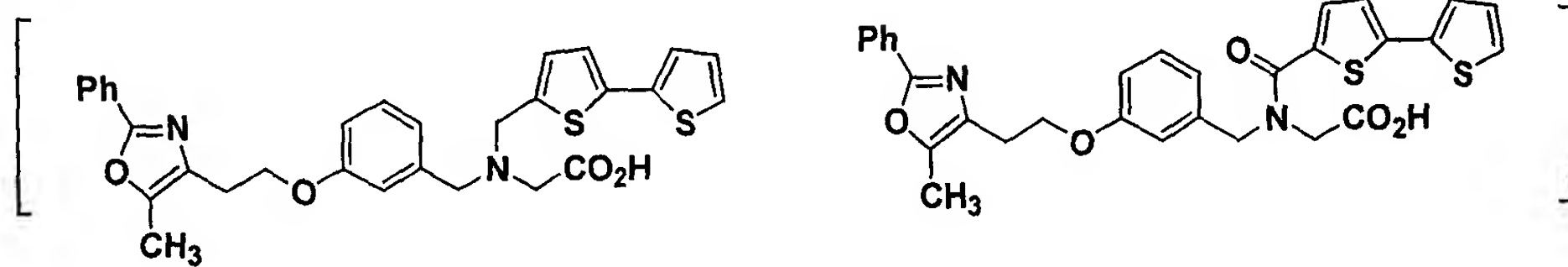
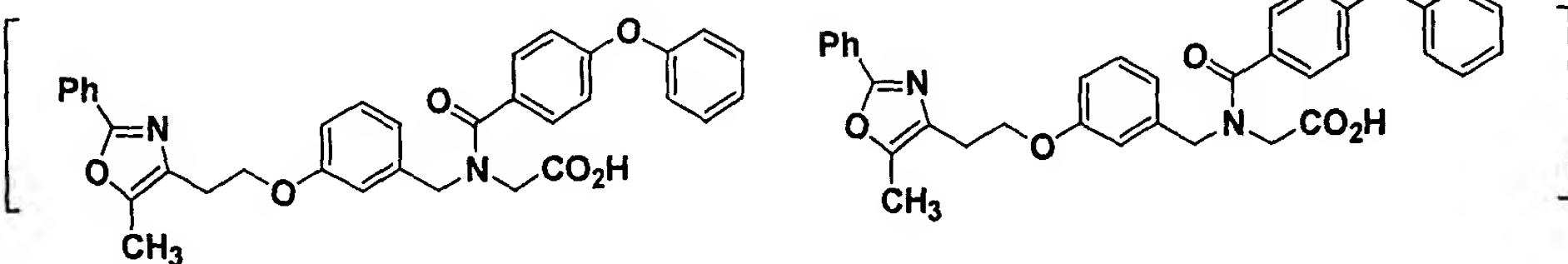
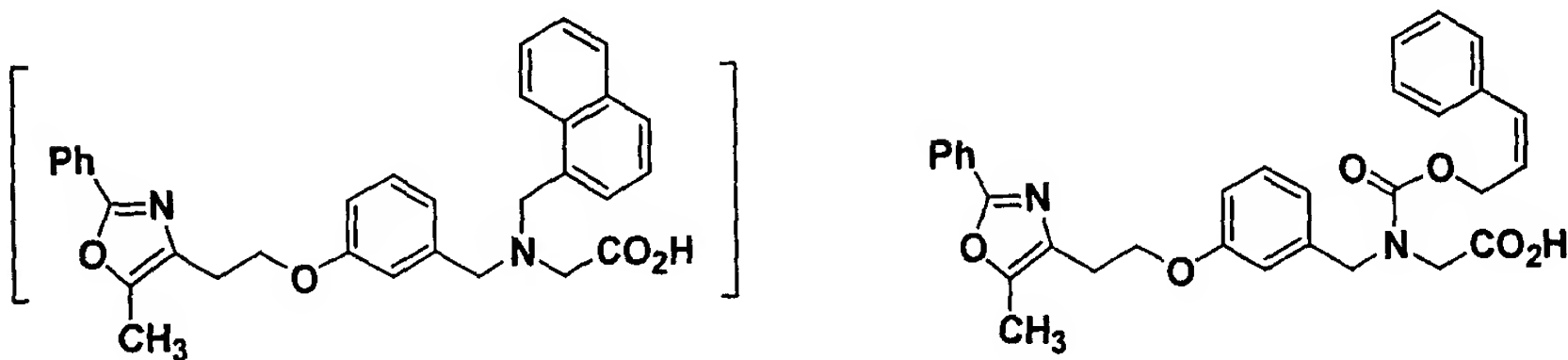
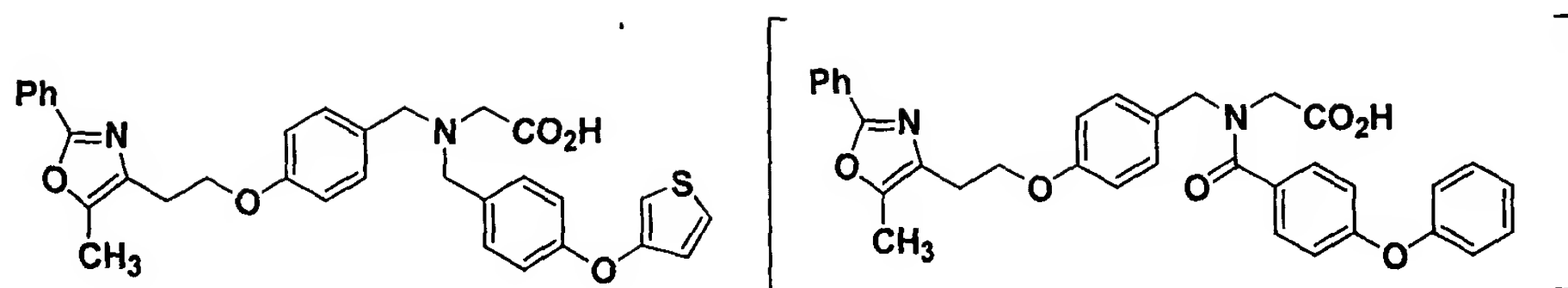




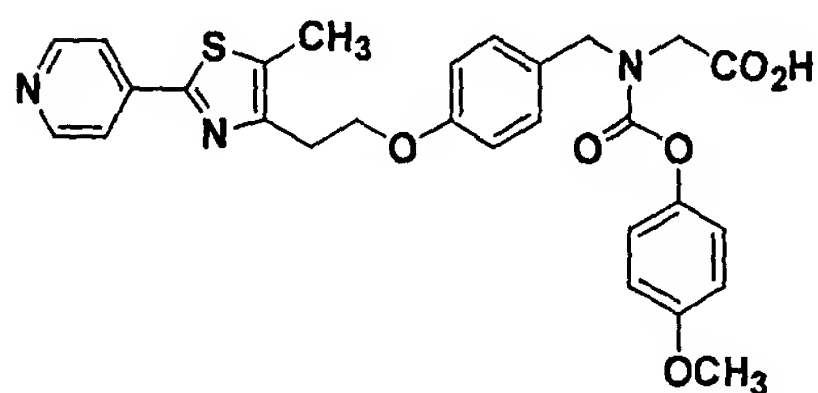
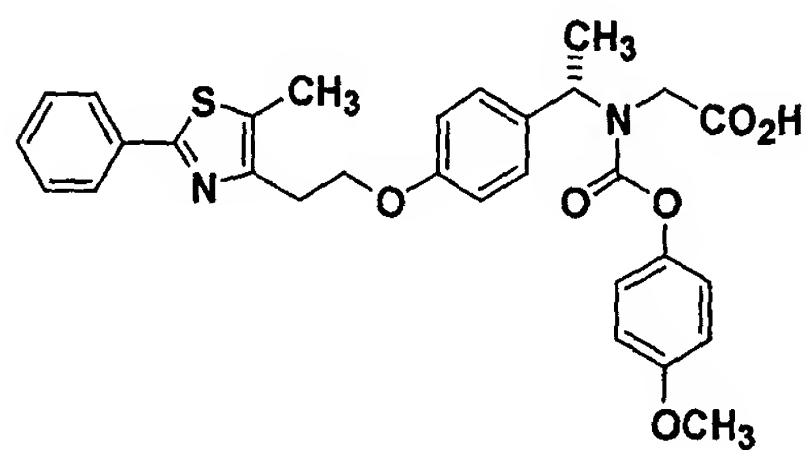
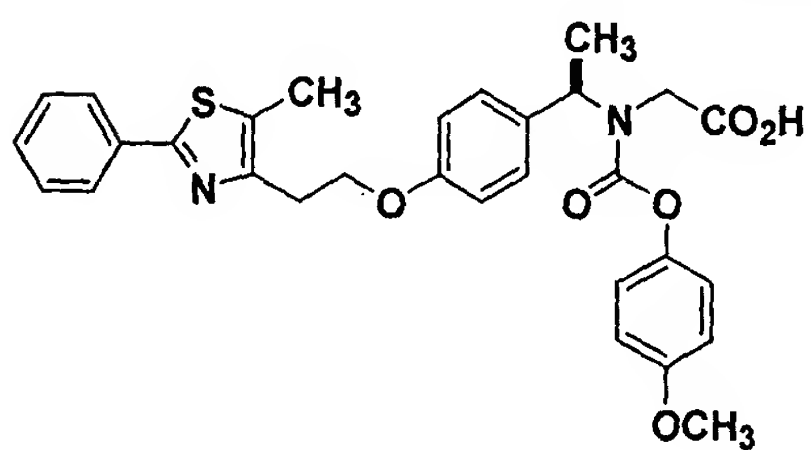
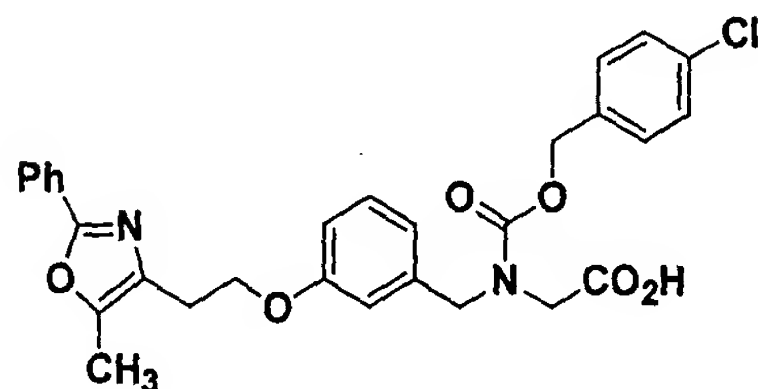
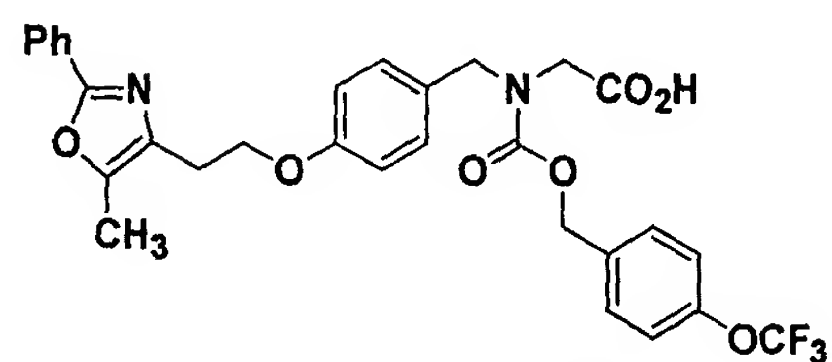
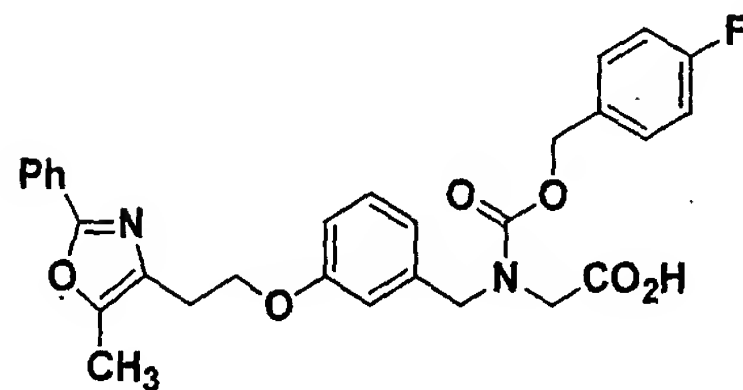
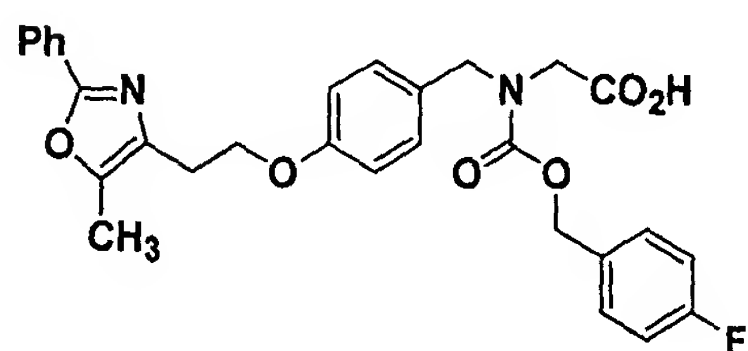
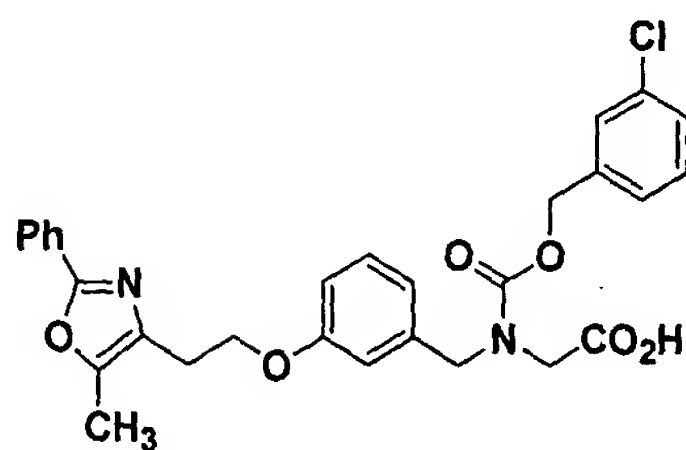
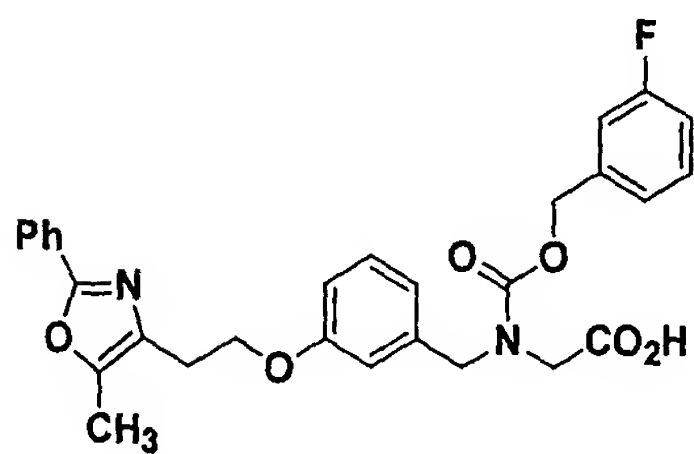
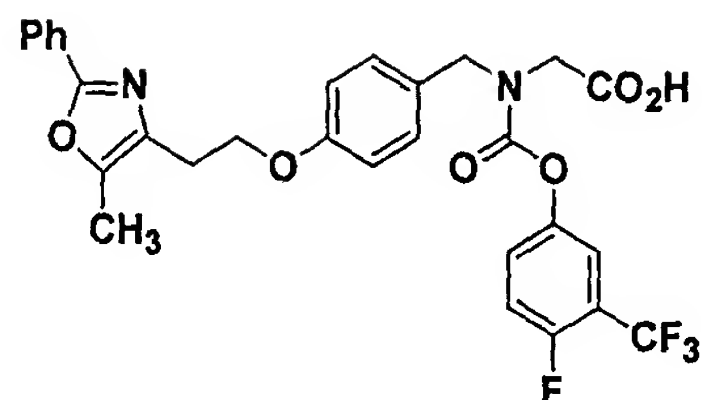
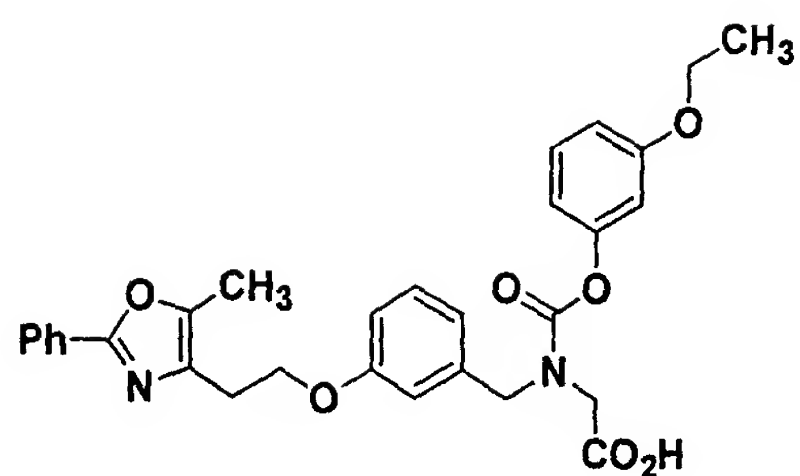




SE LA29a DIV-2

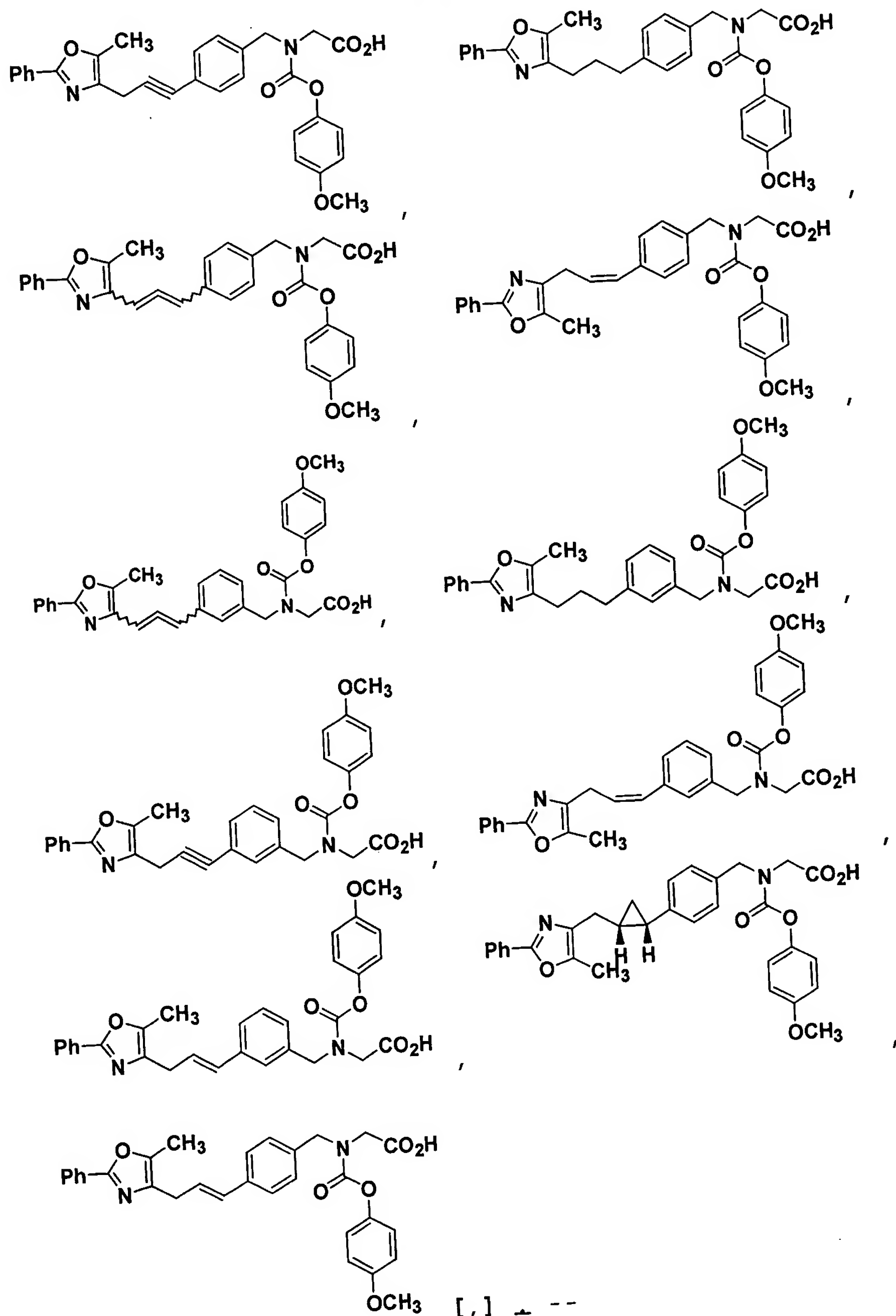


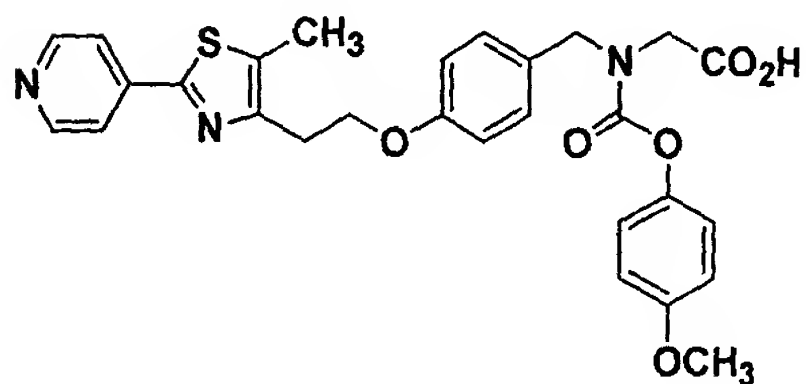
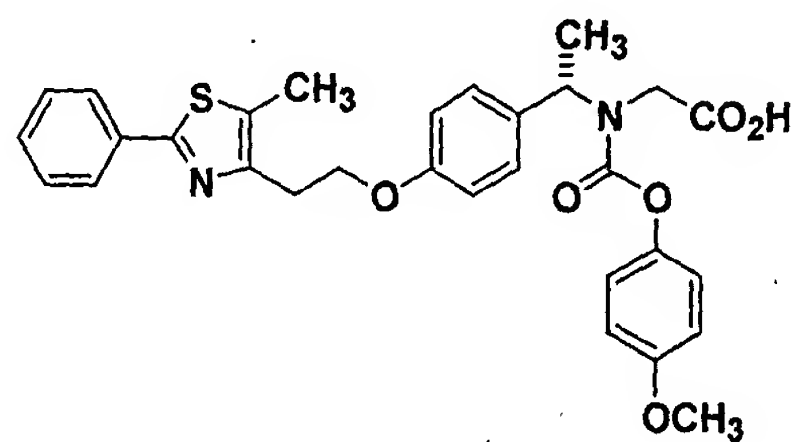
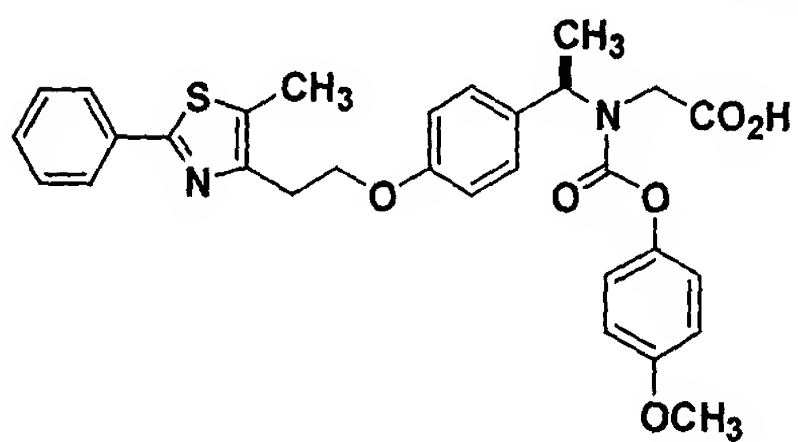
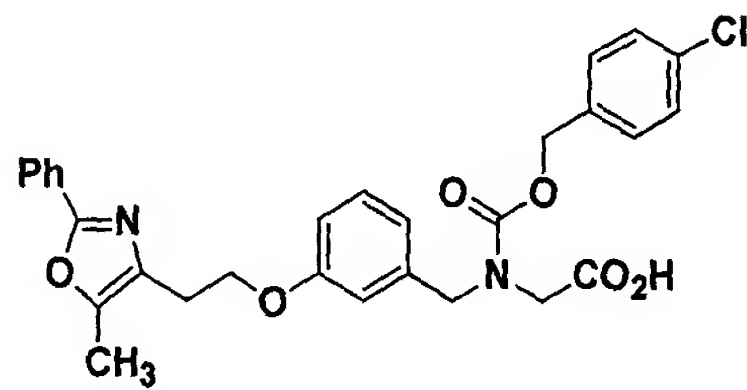
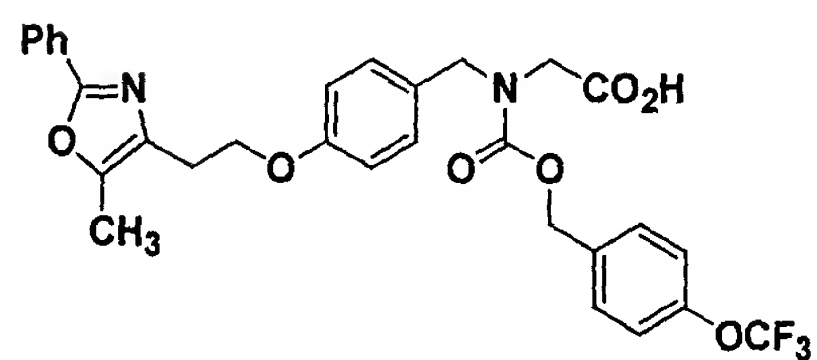
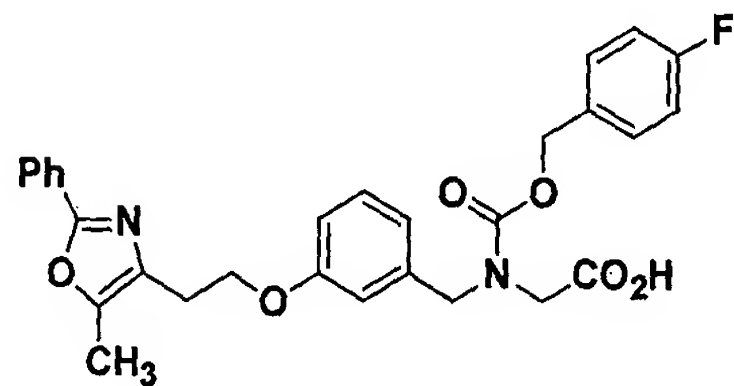
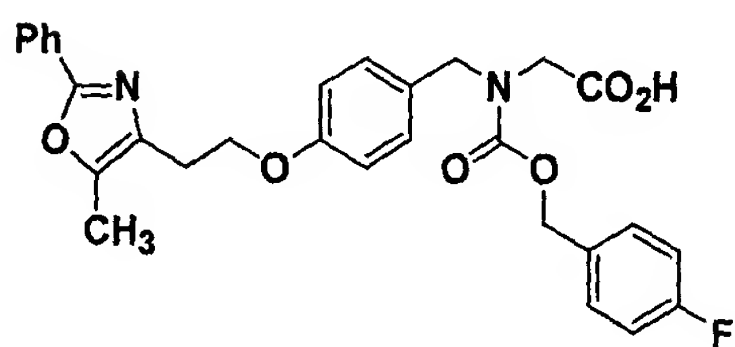
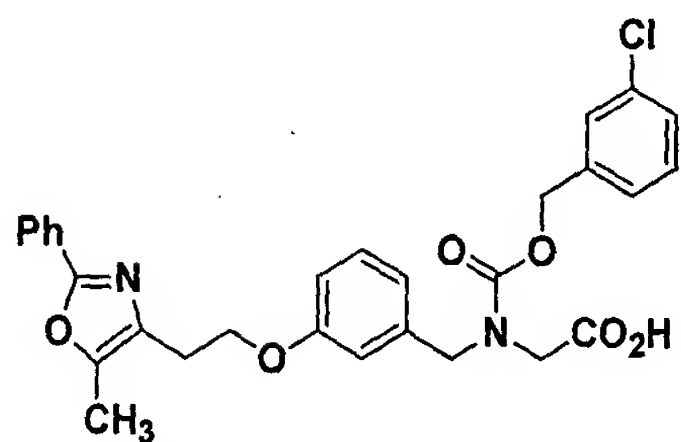
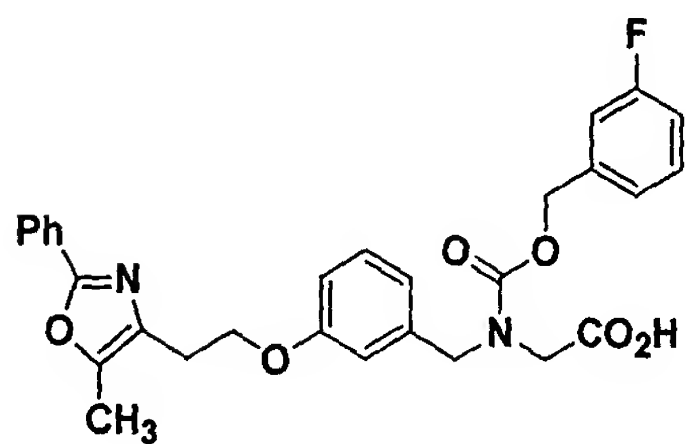
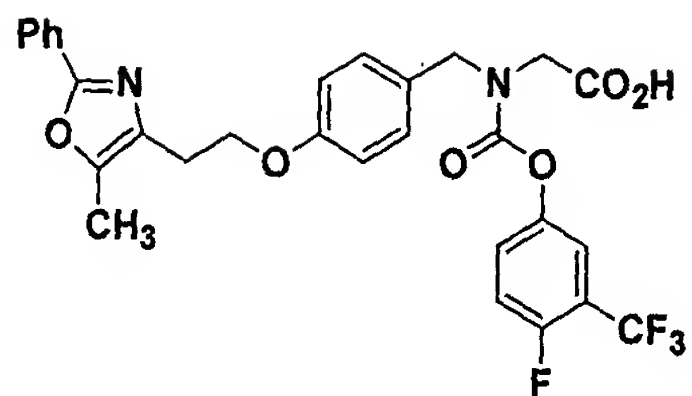
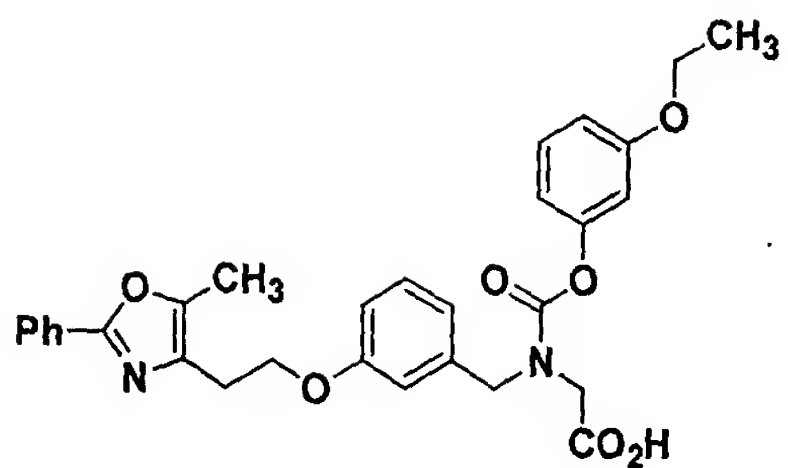




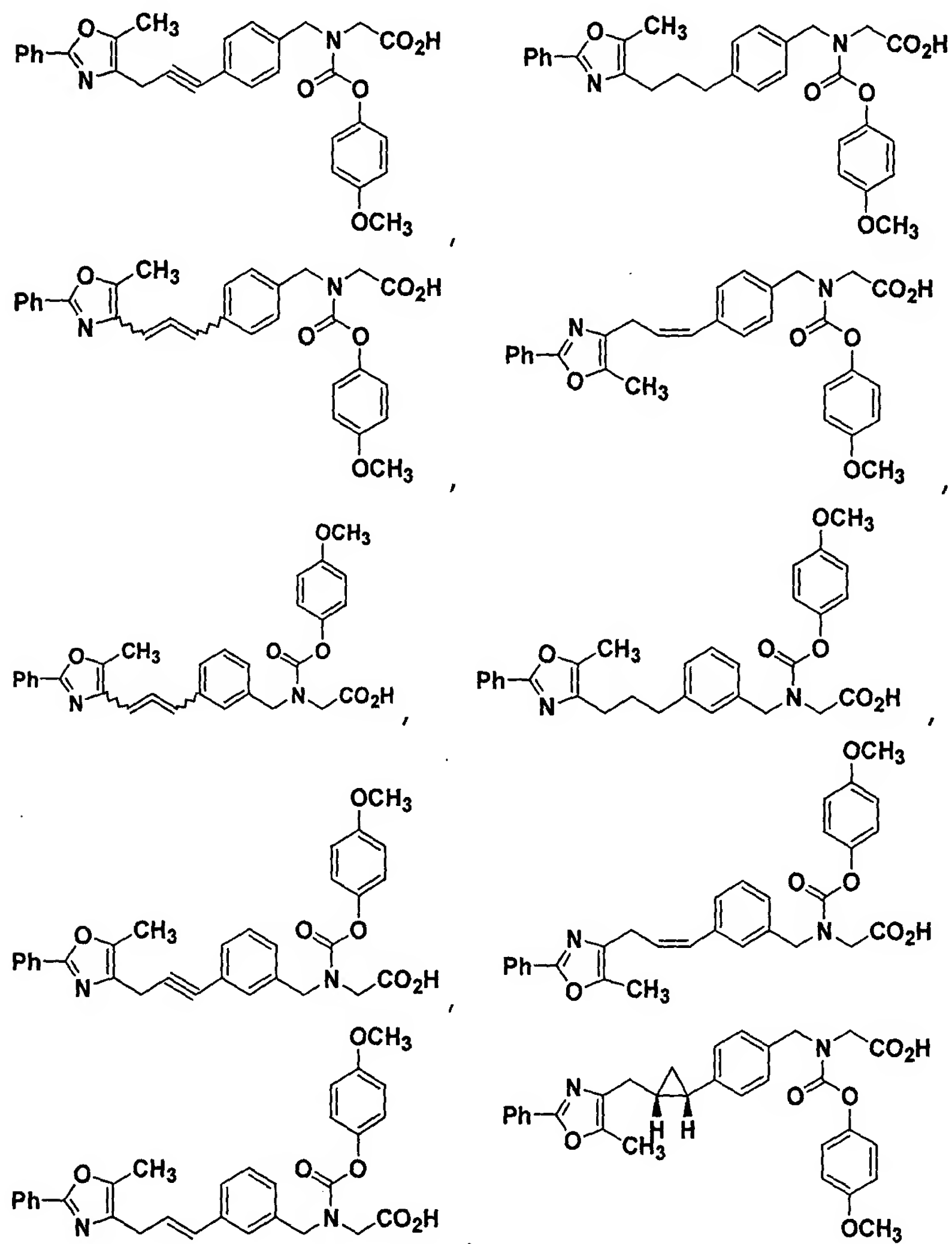


18. The [compound] method as defined in Claim 34 [1 having]  
wherein the compound employed has the structure





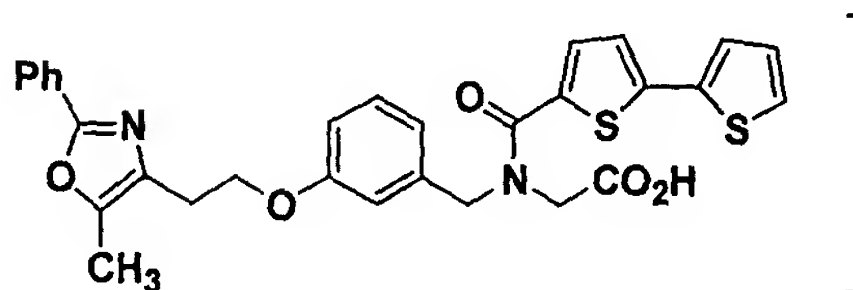
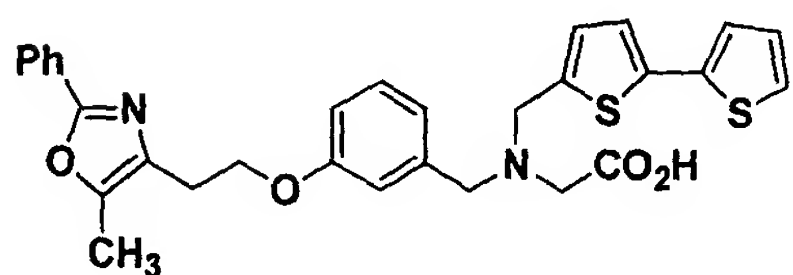
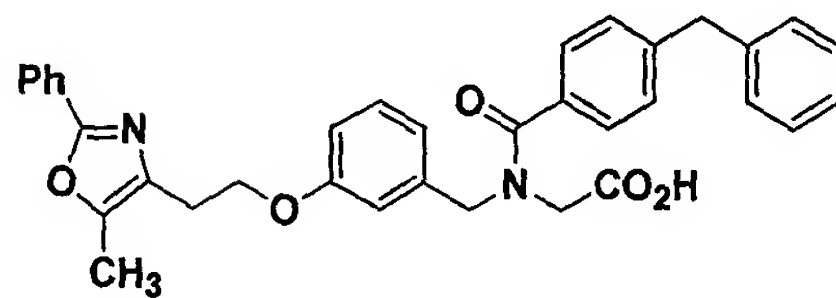
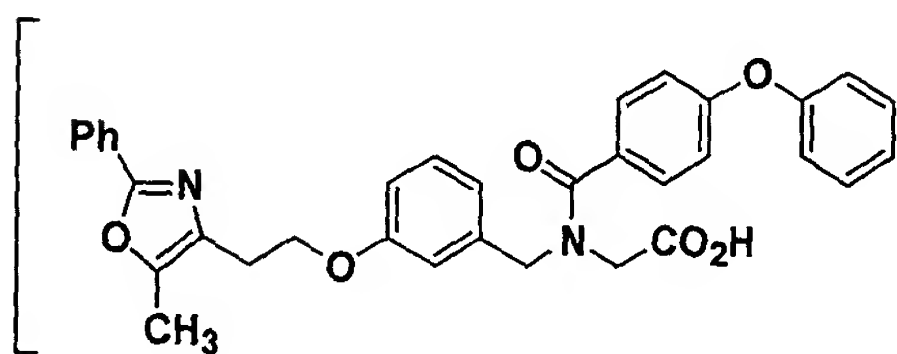
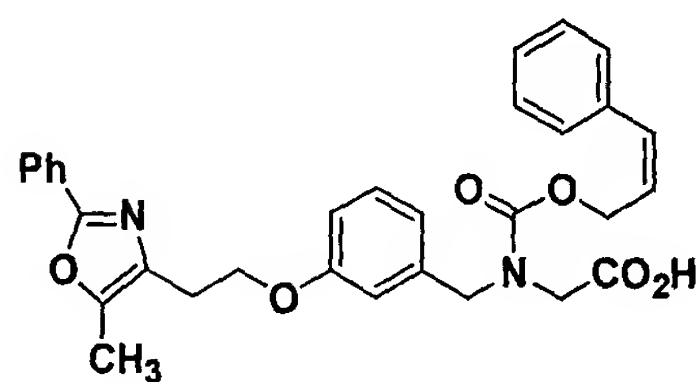
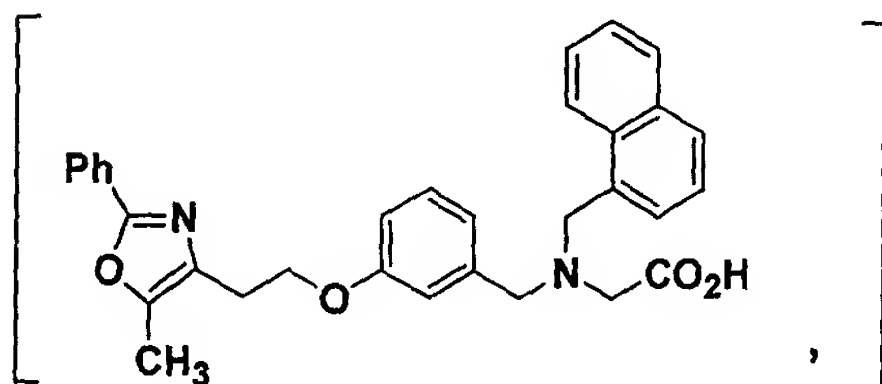
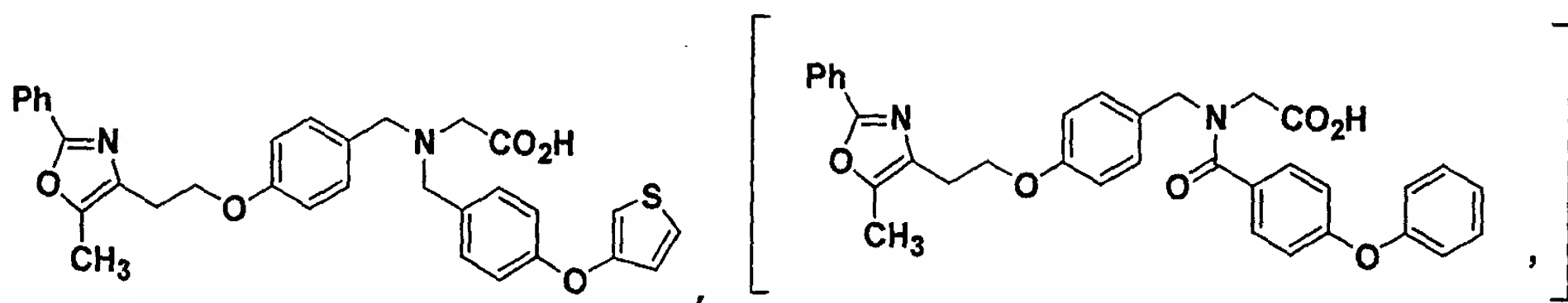
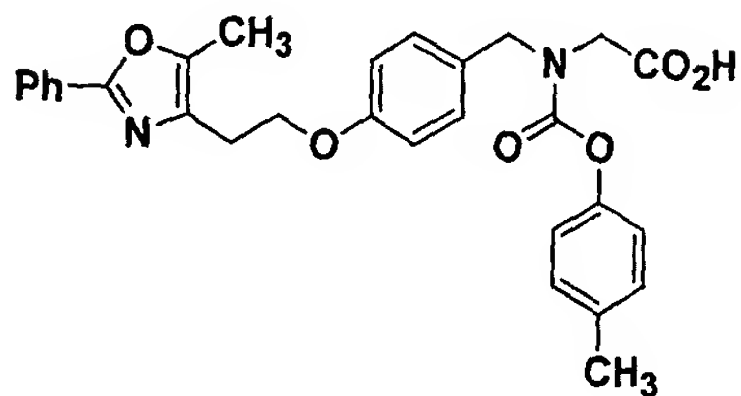
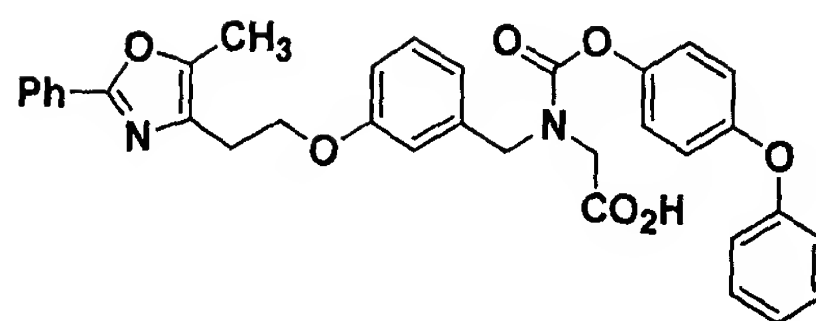
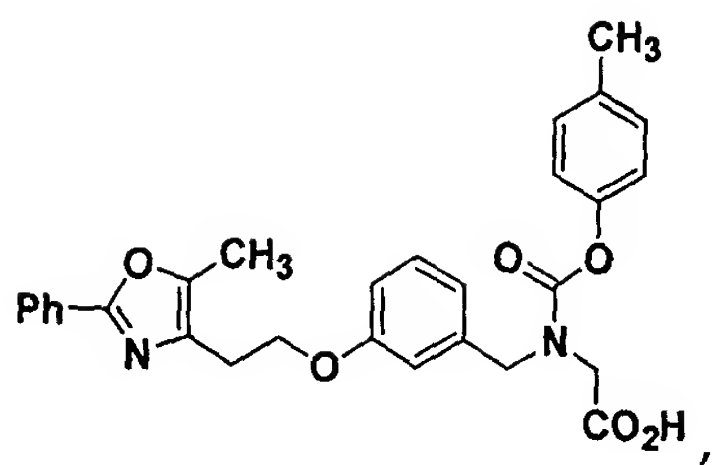
18. The [compound] method as defined in Claim 34 [1 having] wherein the compound employed has the structure

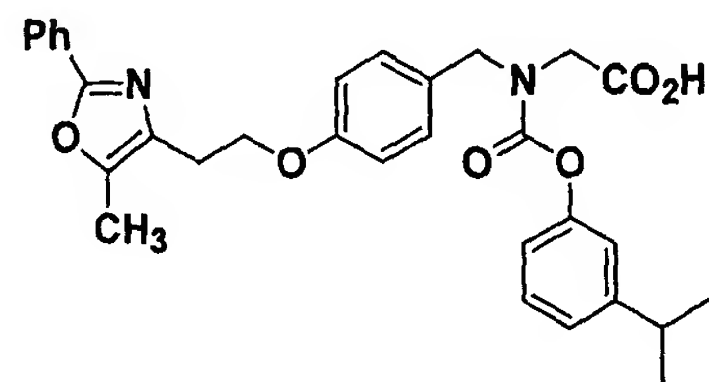
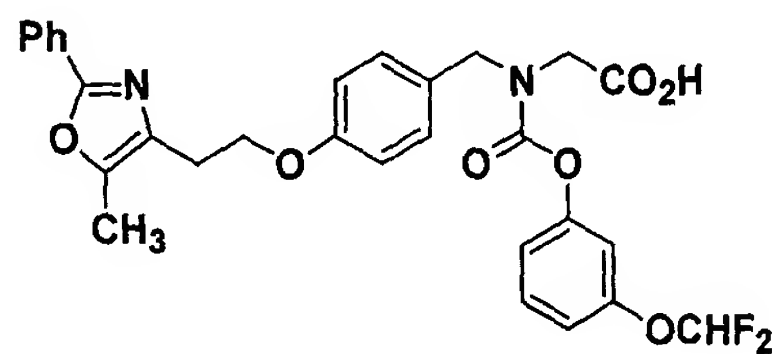
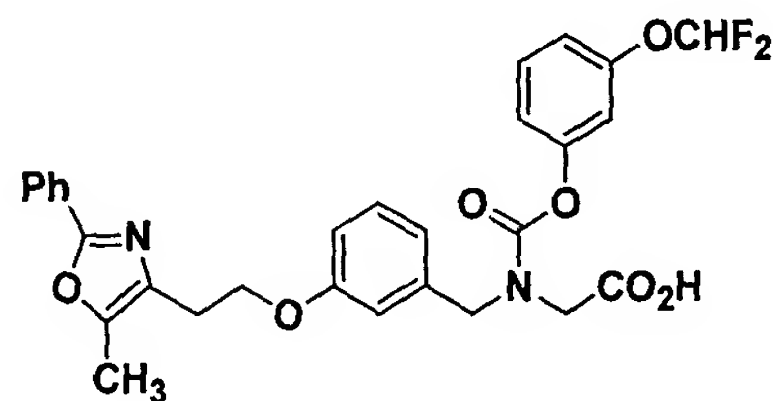
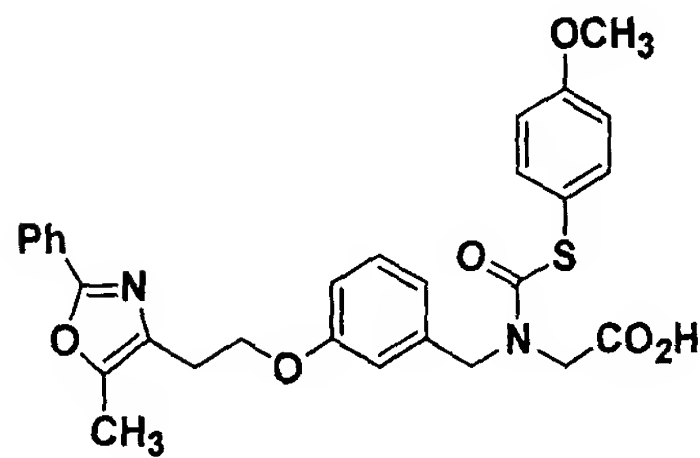
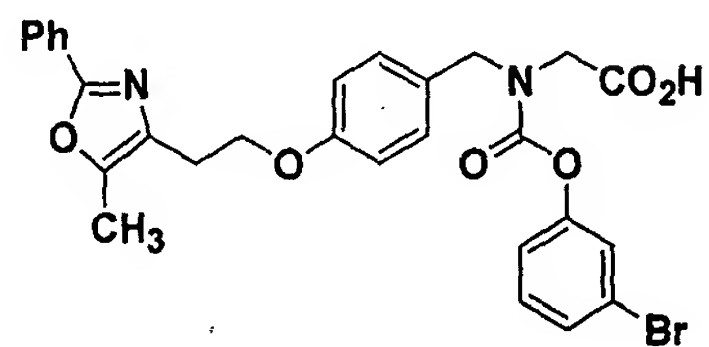
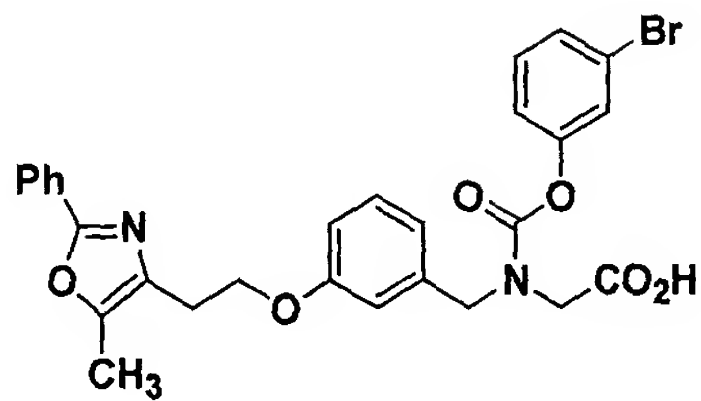
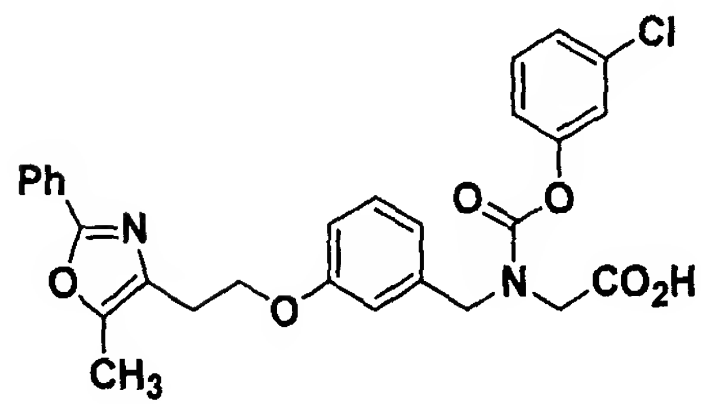
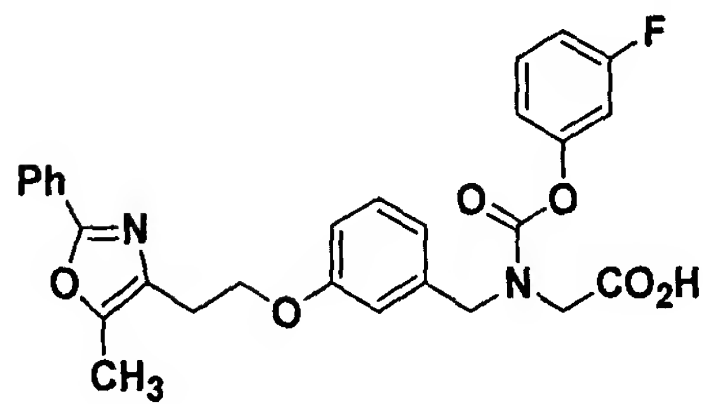
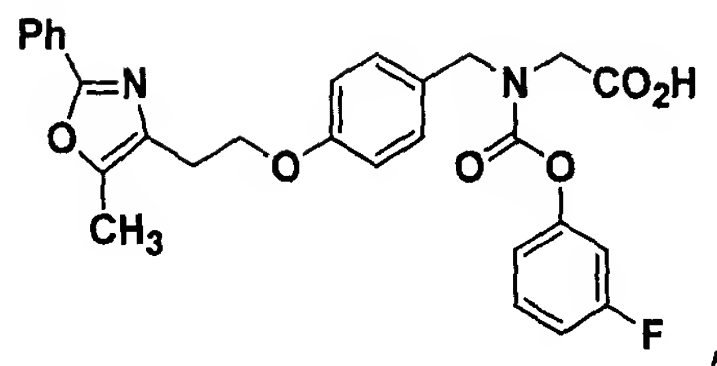
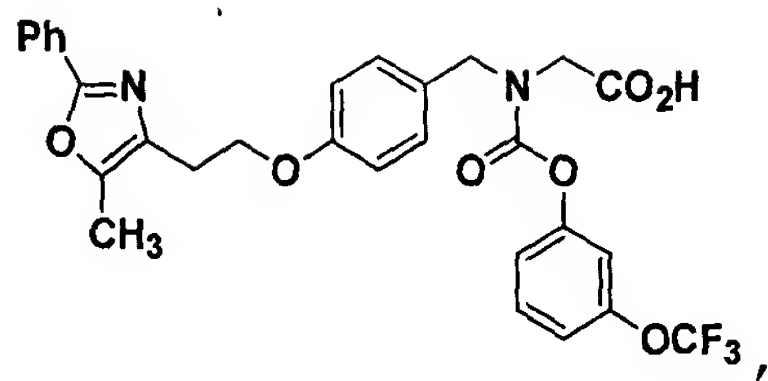


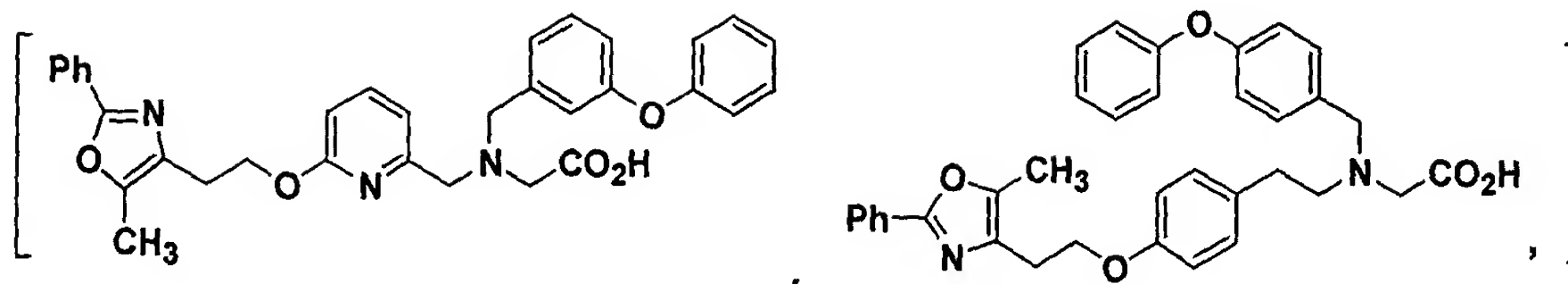


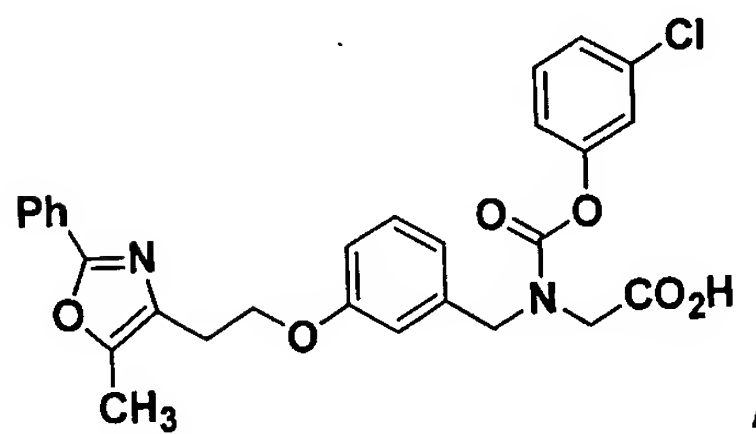
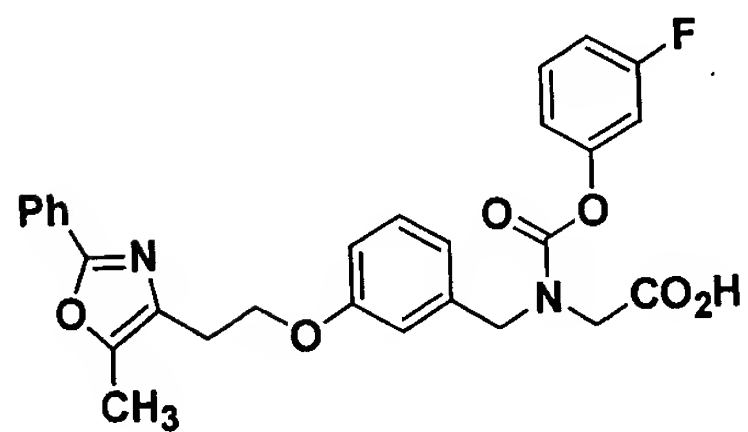
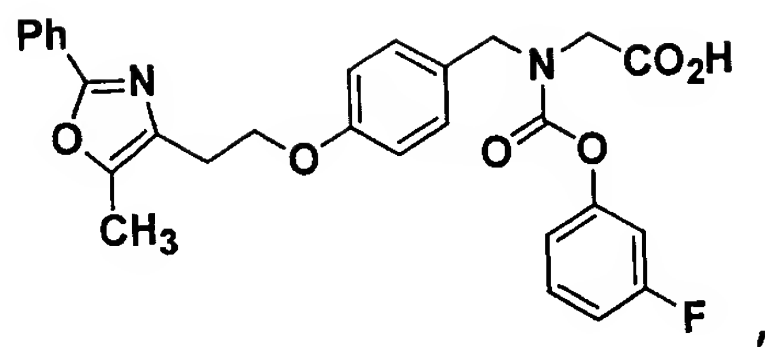
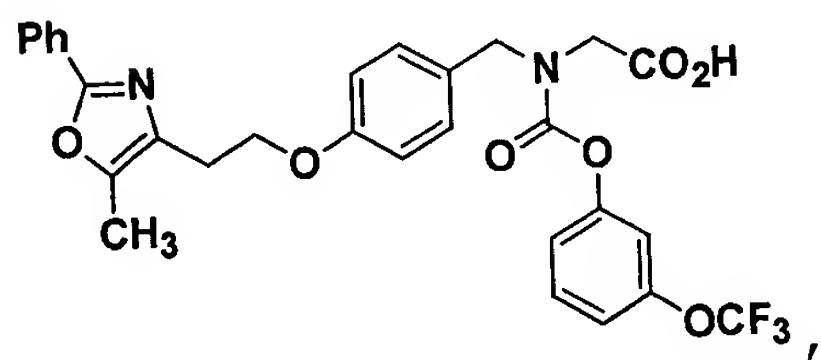
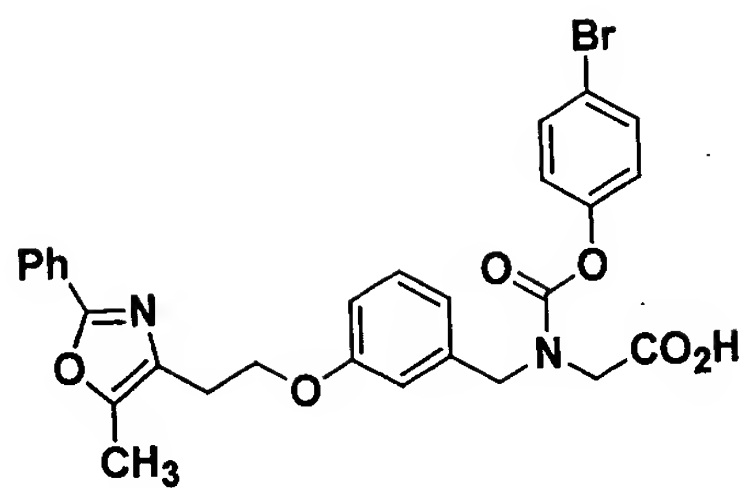
compound employed has [having] the structure



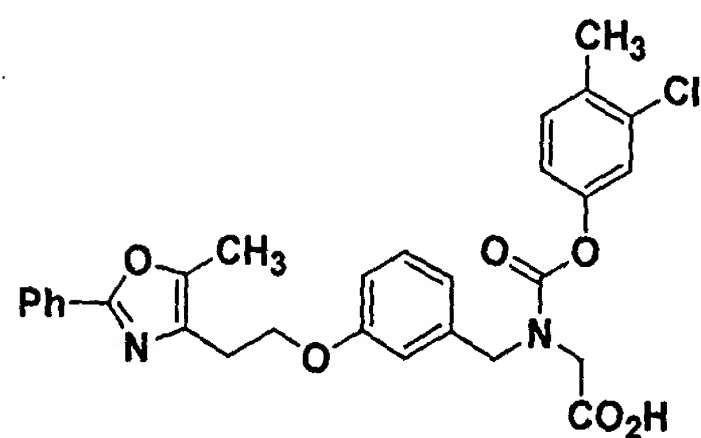
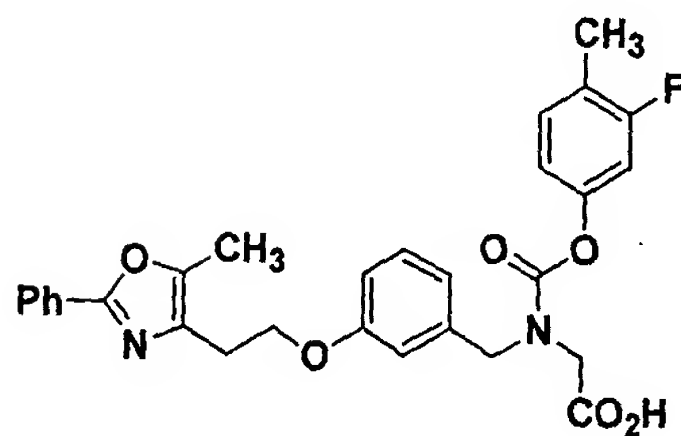
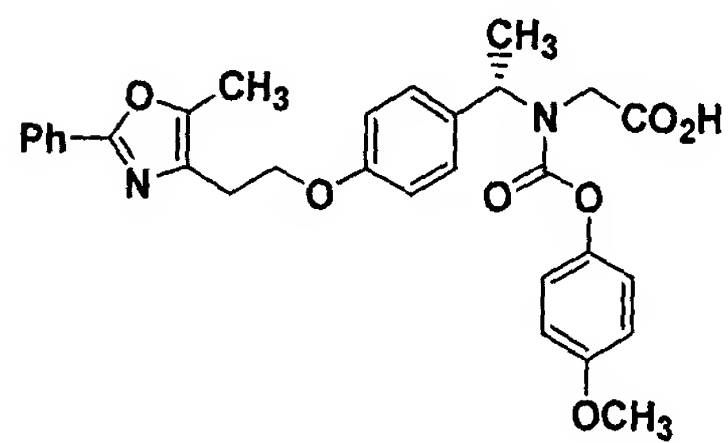
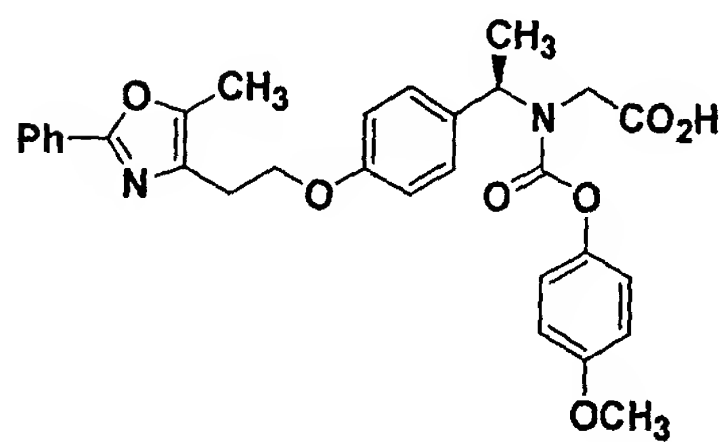
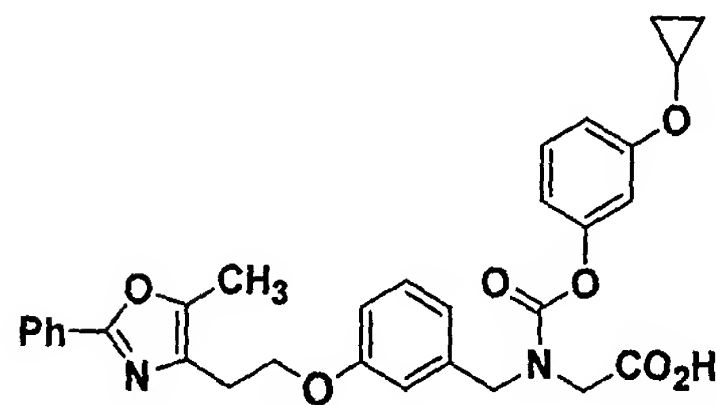
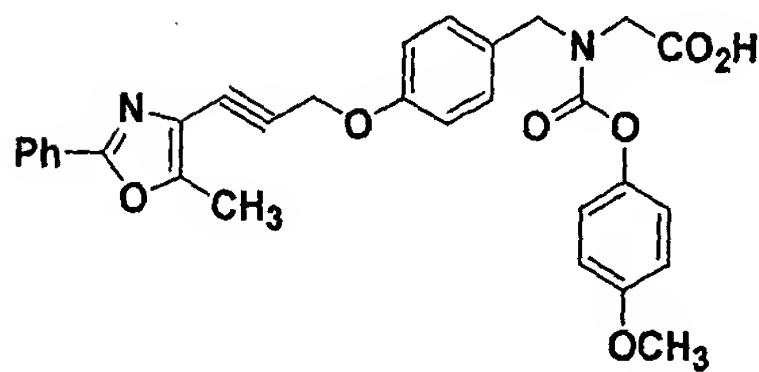
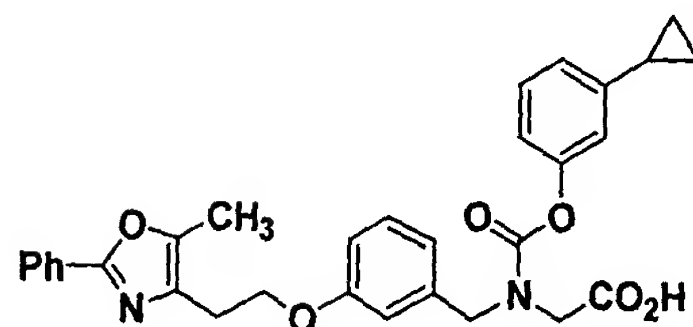
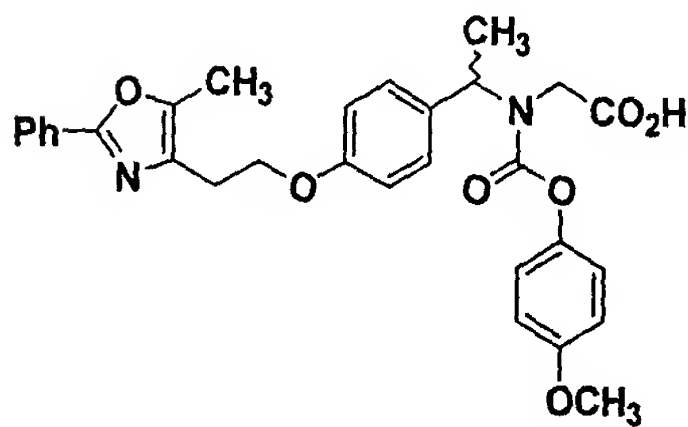
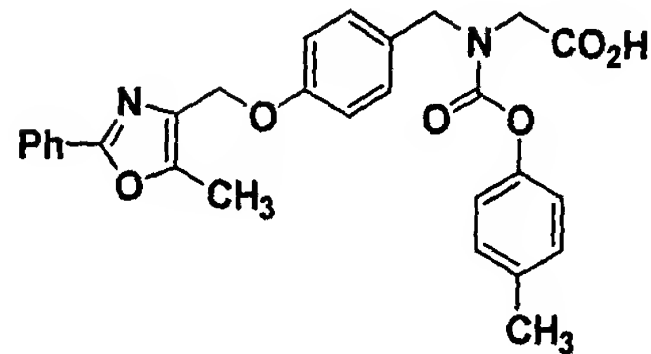
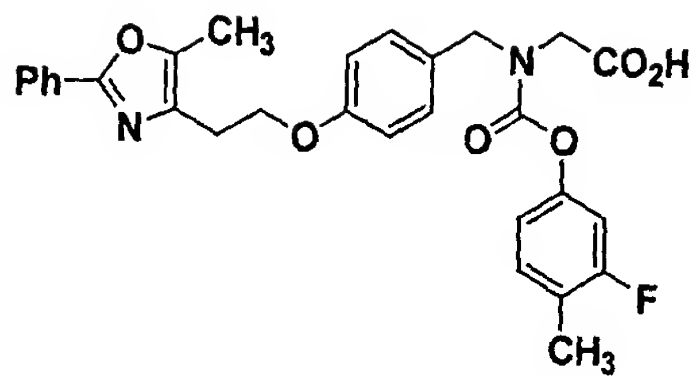


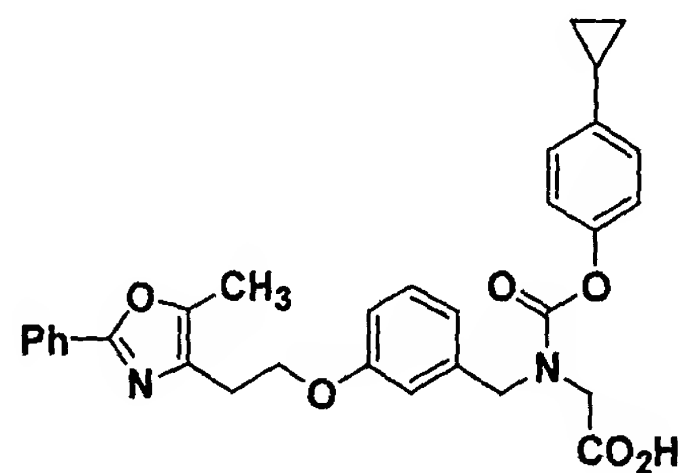
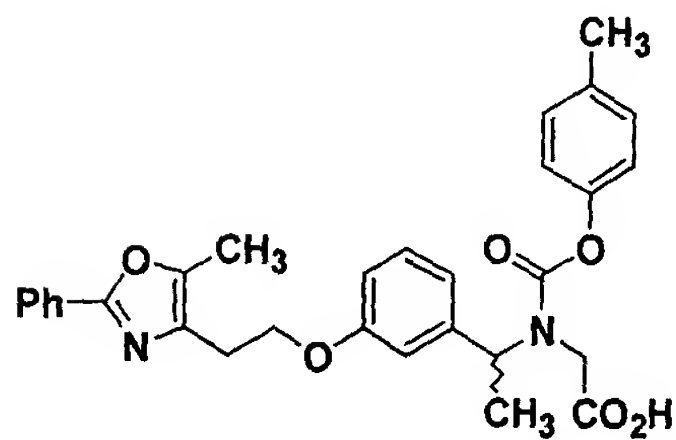
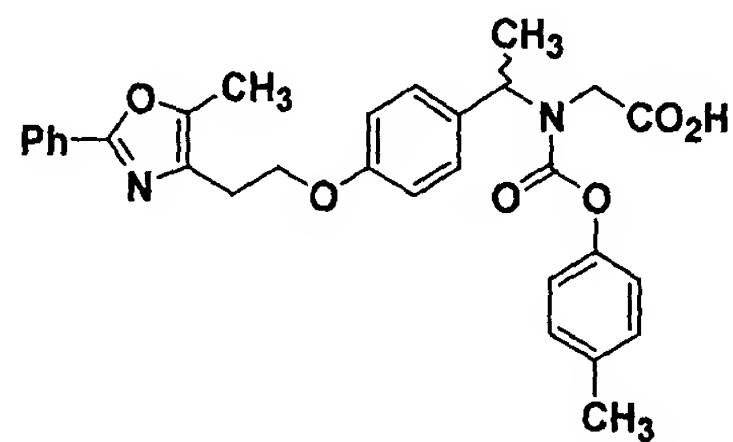
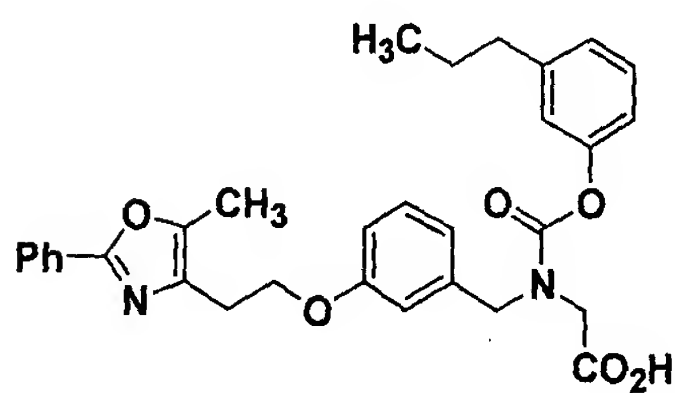
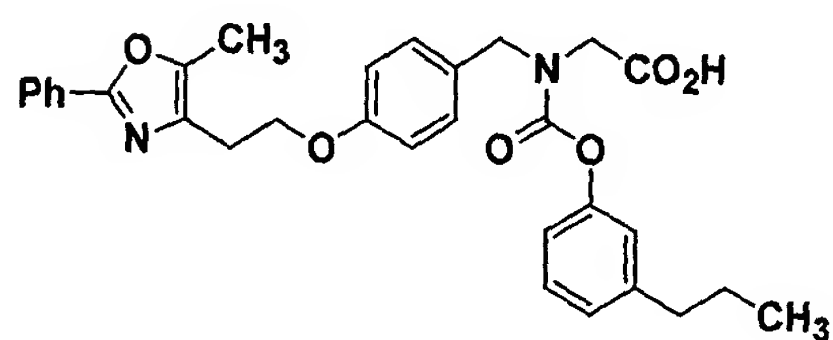
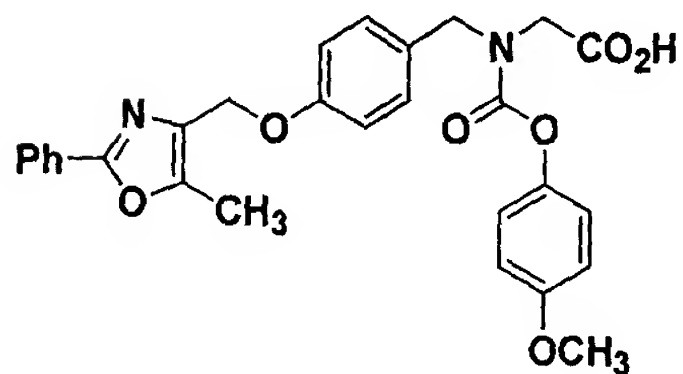
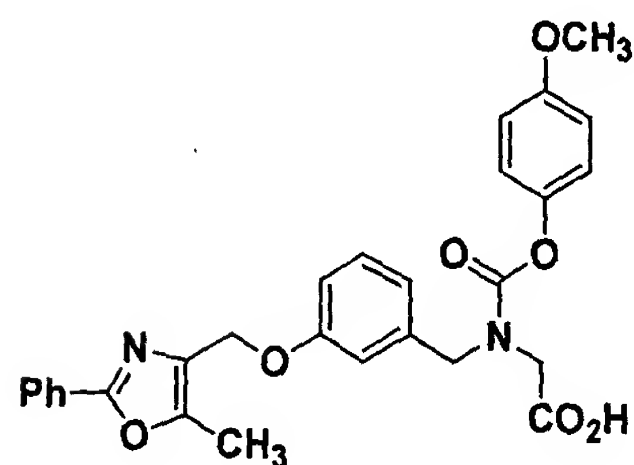
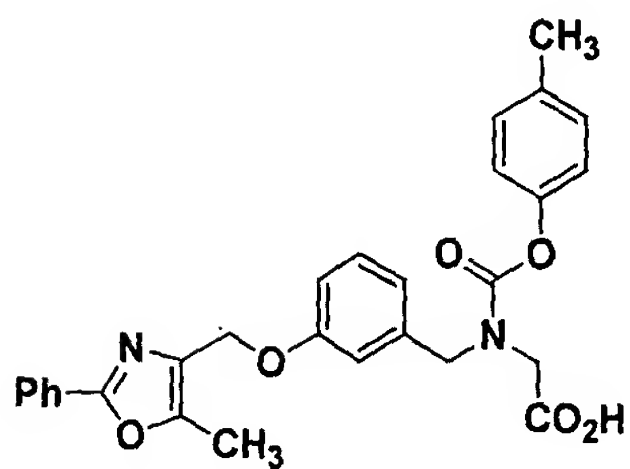
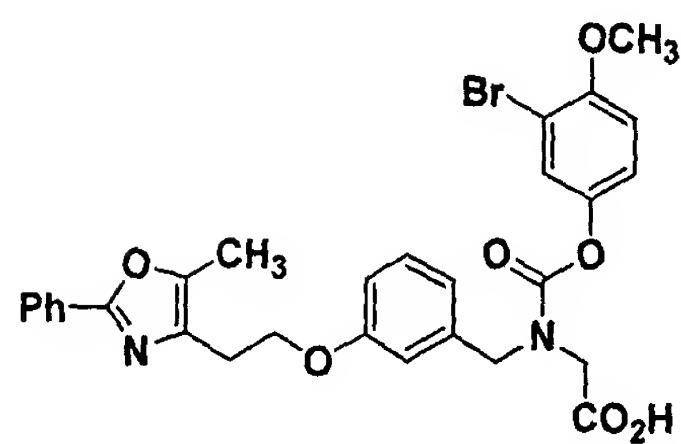
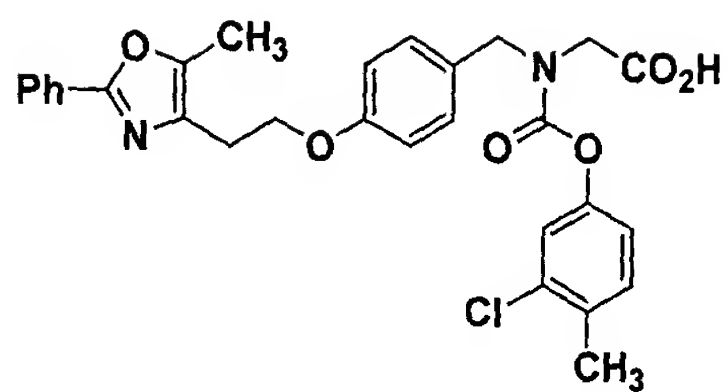


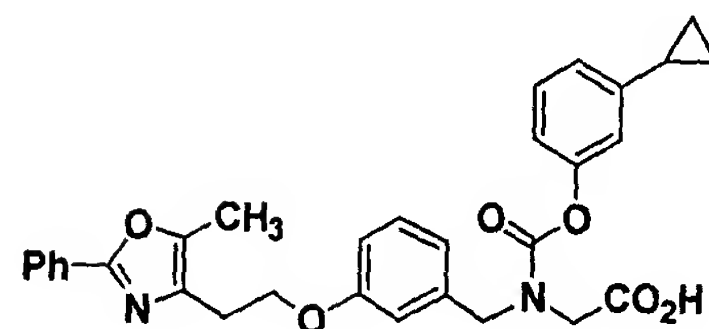
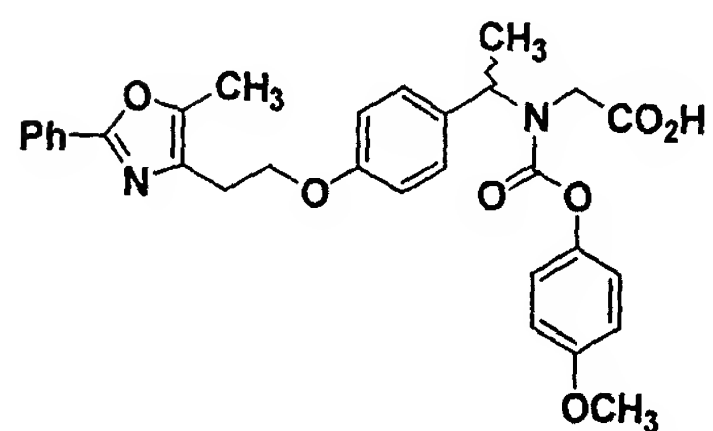
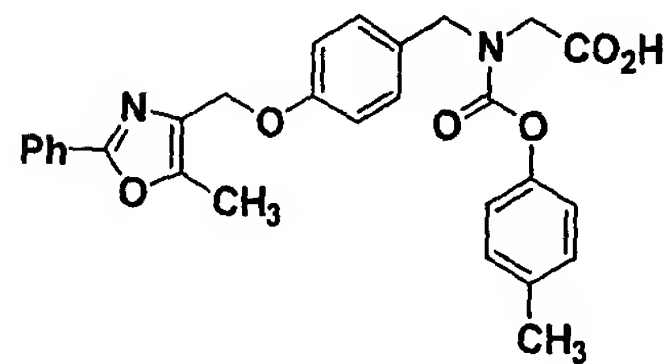
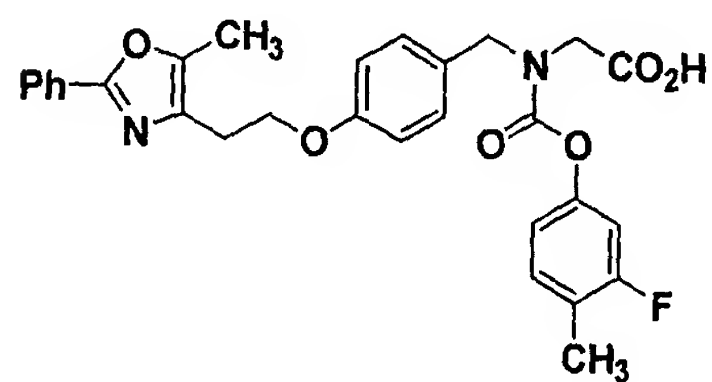
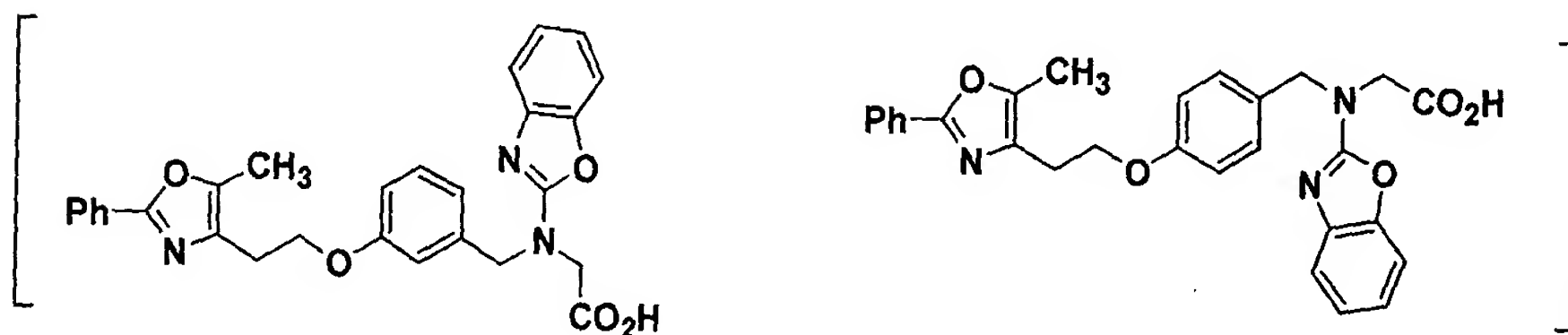
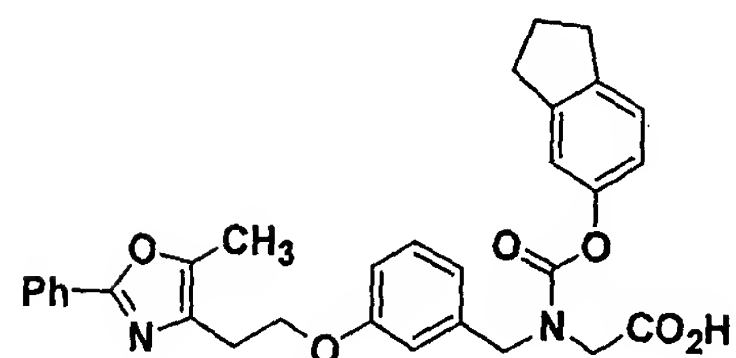
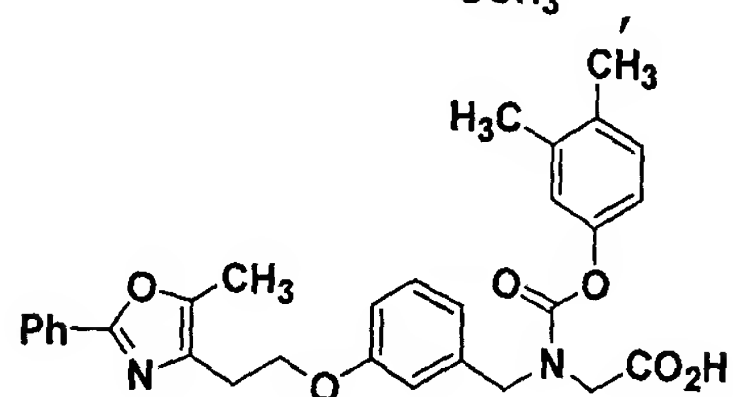
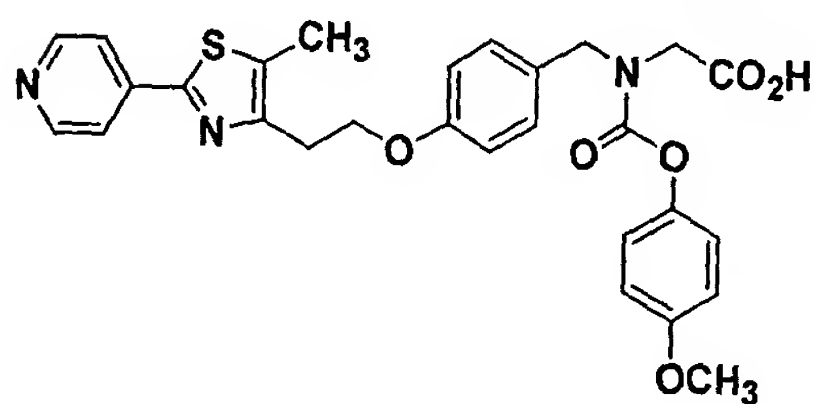
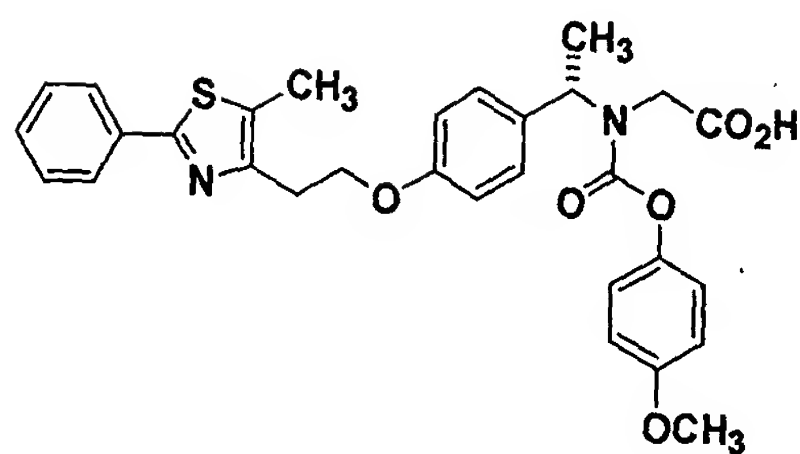




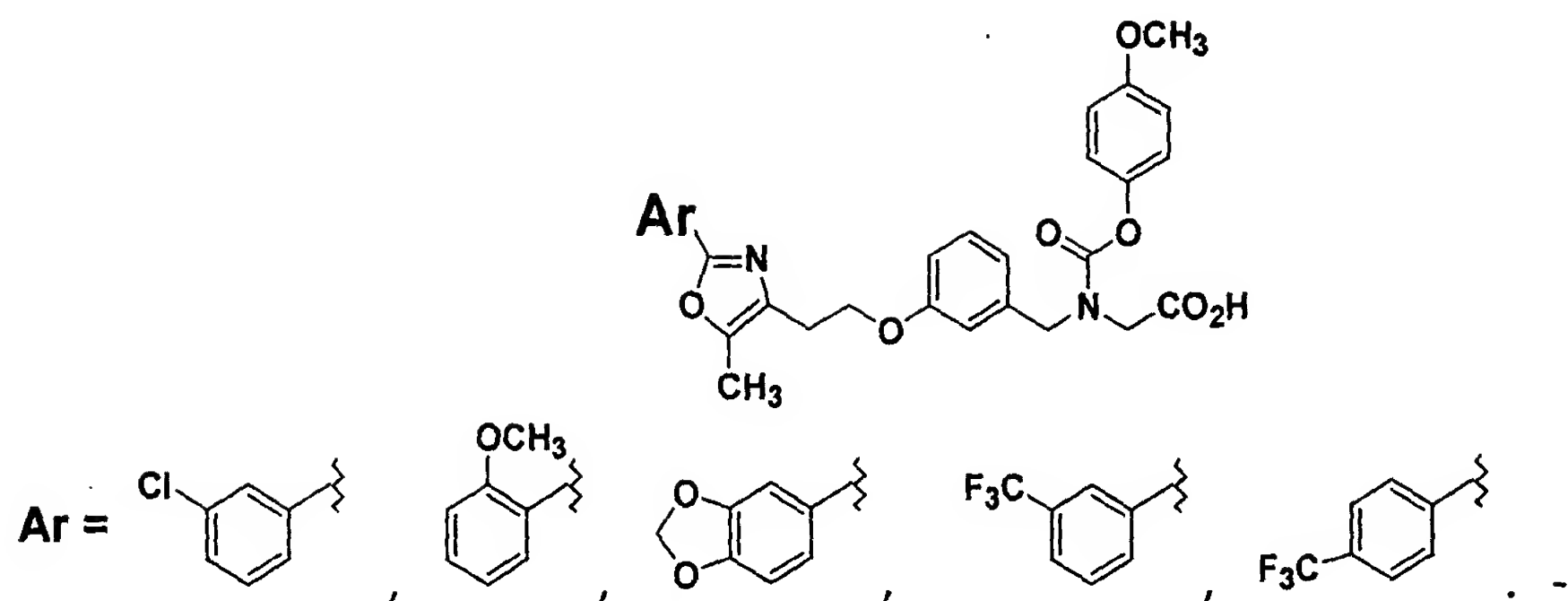




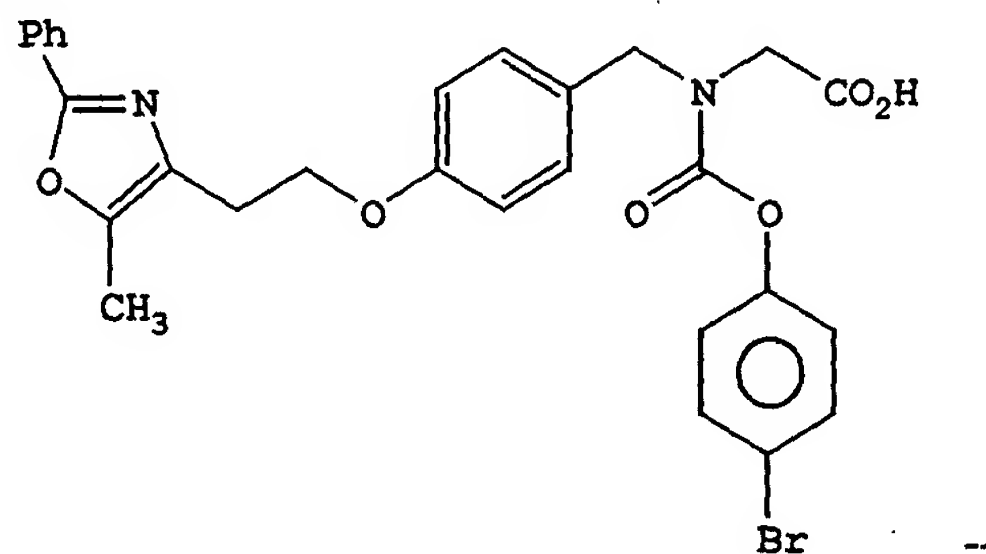




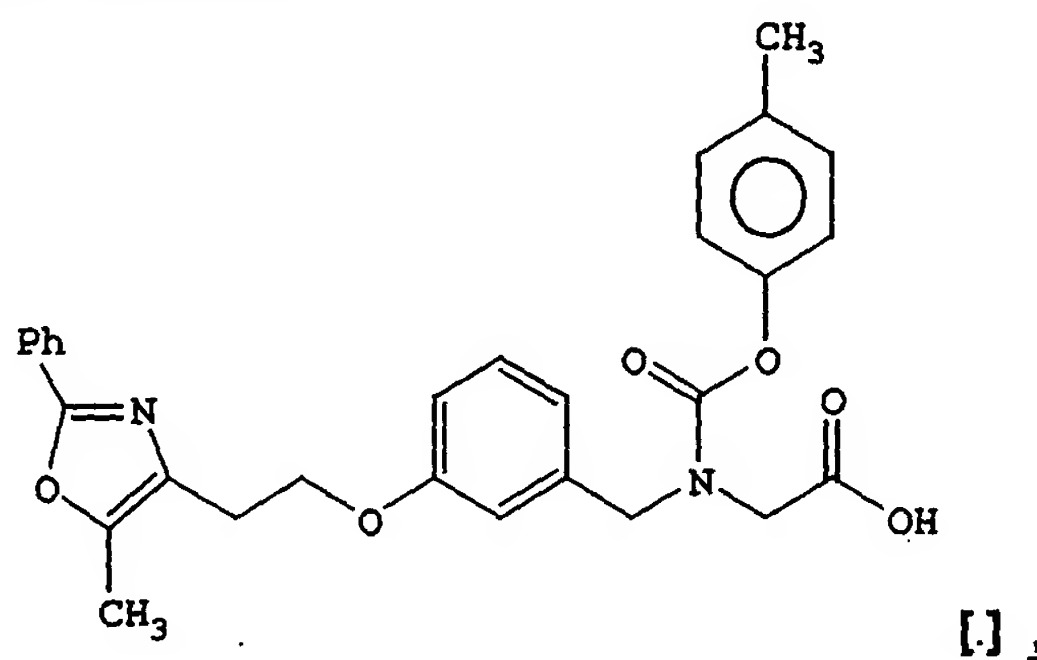


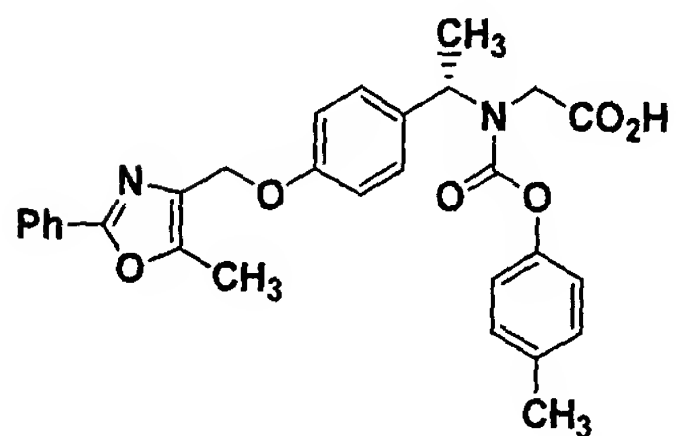
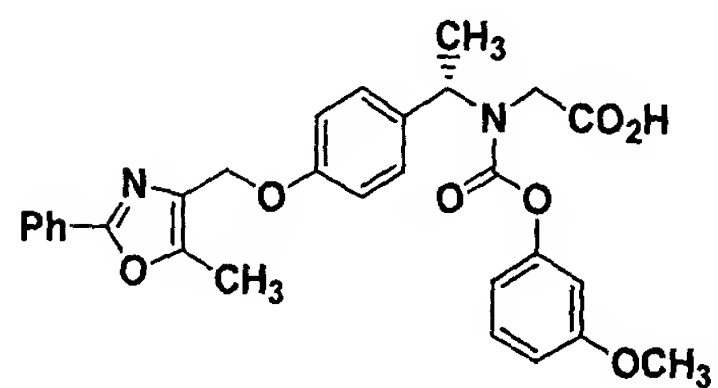
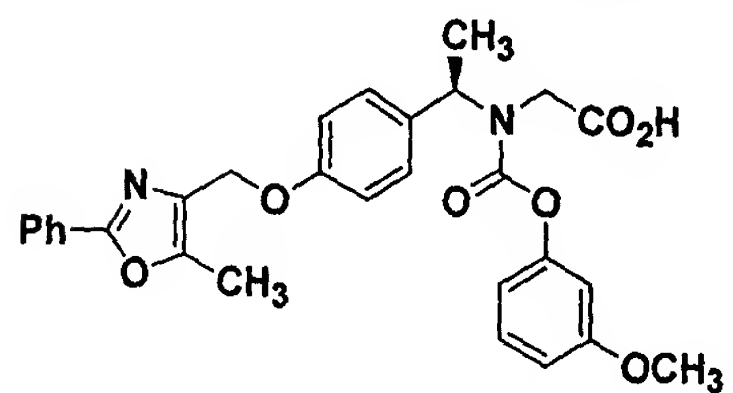
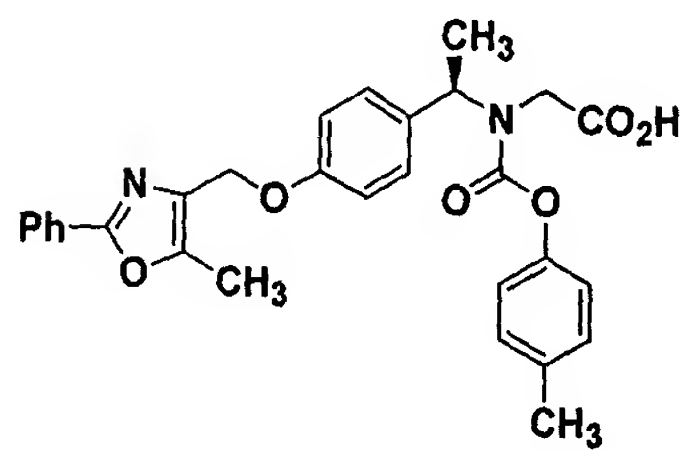
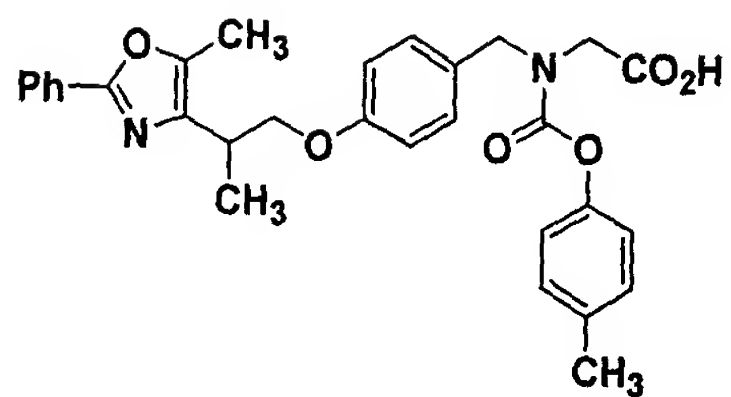


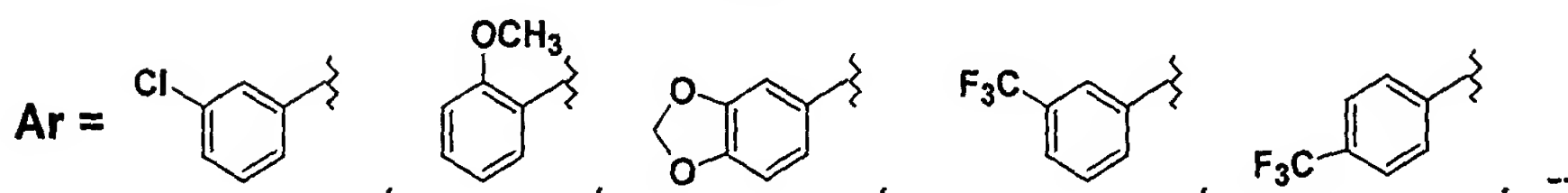
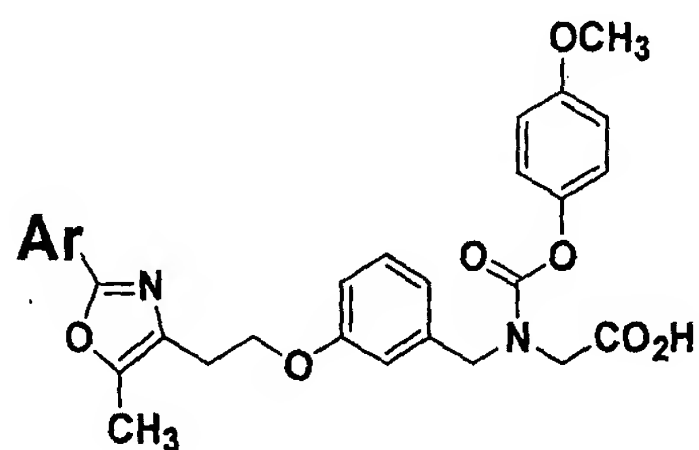
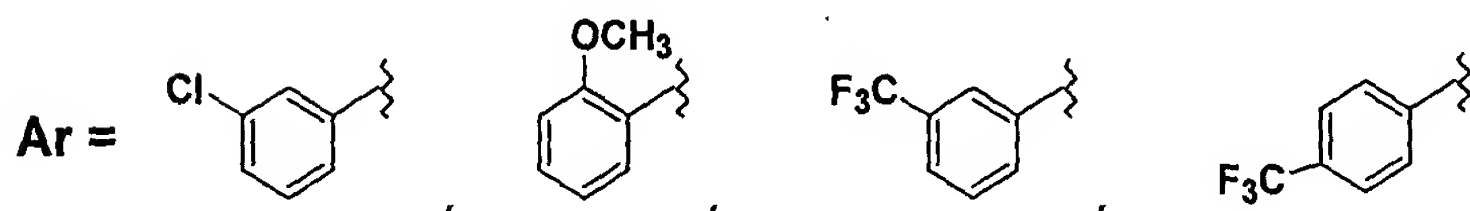
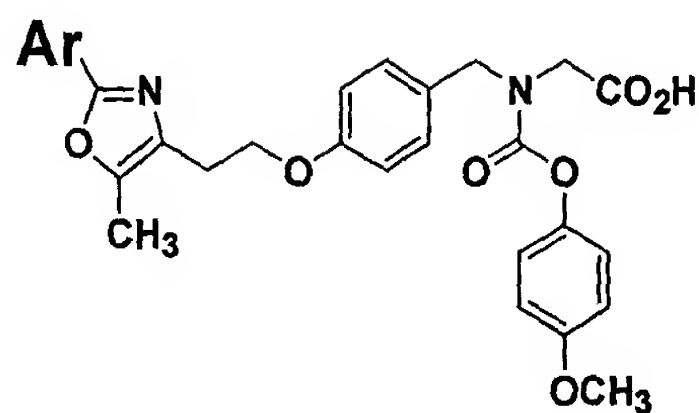
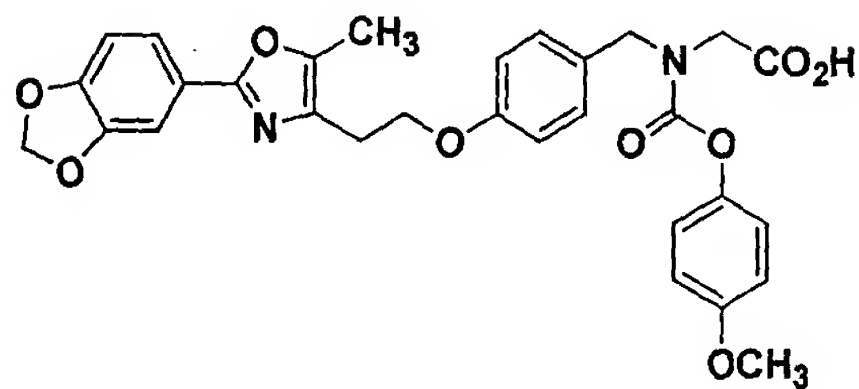
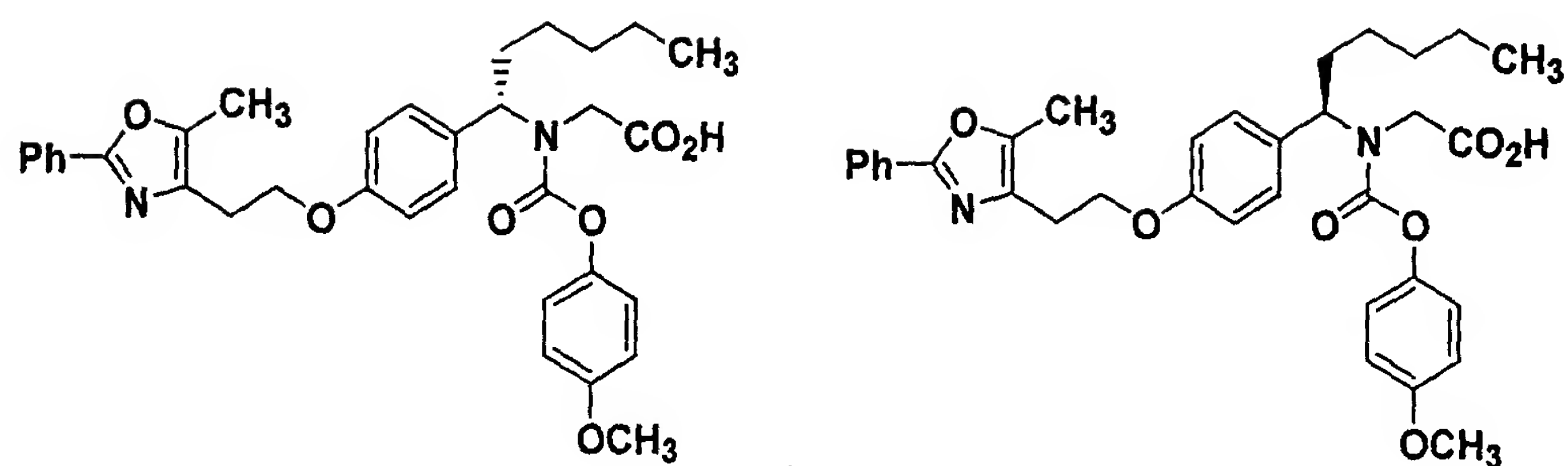
--21. (Amended) The [compound] method as defined in Claim [1 having] 55 wherein the compound employed has the structure



--22. (Amended) The [compound] method as defined in Claim [1 having] 55 wherein the compound employed has the structure







--21. (Amended) The [compound] method as defined in Claim [1 having] 55 wherein the compound employed has the structure

CC1=C(C=C(C=C1C2=CC=CC=C2)OC3=CC=CC=C3)N=C(C=C3C(=C(C=C(C=C3)C)OC4=CC=CC=C4)OC5=CC=CC=C5)CCC1=C(C(=O)O)C(=O)OCC1C(=O)Oc2ccc(cc2)C(=O)OCC1=CC=C(C=C1)COc2cc(C)c(Oc3ccccc3)n2

X is CH;



R<sup>2</sup> is H, alkyl, alkoxy, halogen, amino or substituted amino;

R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> are the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

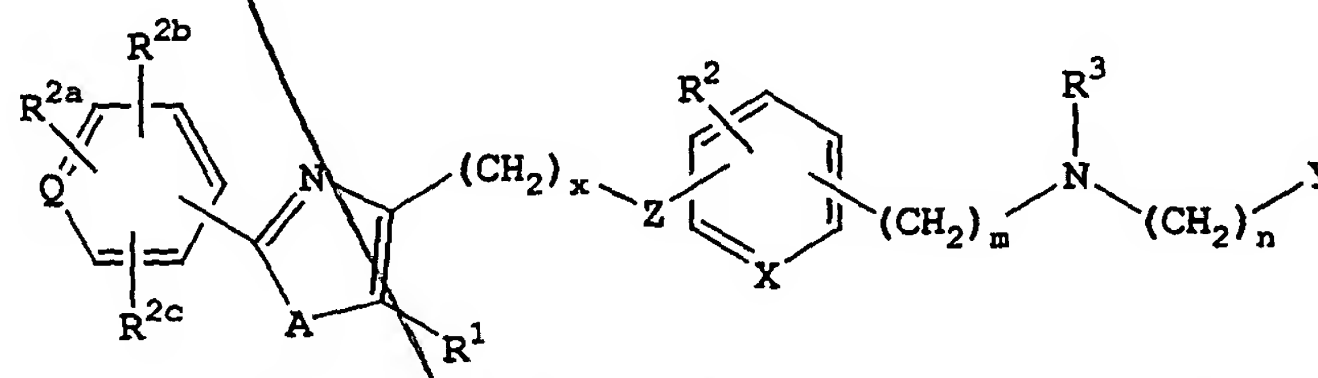
R<sup>3</sup> is aryloxy carbonyl, alkyloxy carbonyl, alkynyloxy carbonyl, alkenyloxy carbonyl, alkyl(halo)aryloxy carbonyl, alkyloxy(halo)aryloxy carbonyl, cycloalkylaryloxy carbonyl, cycloalkyloxyaryloxy carbonyl, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxy carbonylamino, aryloxy carbonylamino, heteroaryloxy carbonylamino, alkylsulfonyl, alkenylsulfonyl, heteroaryloxy carbonyl, cycloheteroalkyloxy carbonyl, heteroarylalkenyl, hydroxyalkyl, alkoxy, alkoxyaryloxy carbonyl, arylalkyloxy carbonyl, alkylaryloxy carbonyl, alkynyloxy carbonyl, haloalkoxyaryloxy carbonyl, alkoxy carbonylaryloxy carbonyl, aryloxyaryloxy carbonyl, arylalkenyloxy carbonyl, heteroaryloxyarylalkyl, aryloxyarylalkyloxy carbonyl, aryloxyalkyloxy carbonyl, arylalkylsulfonyl, arylthiocarbonyl, arylalkenylsulfonyl, heteroarylsulfonyl, arylsulfonyl, heteroarylalkoxy carbonyl, heteroarylalkyloxyarylalkyl, arylalkenylarylalkyl, arylalkoxy carbonylheteroarylalkyl, heteroaryloxyarylalkyl, arylalkenylheteroarylalkyl or polyhaloalkylaryloxy carbonyl;

Y is CO<sub>2</sub>R<sup>4</sup> where R<sup>4</sup> is H or alkyl, or a prodrug ester or Y is a C-linked 1-tetrazole, a phosphinic acid of the structure P(O)(OR<sup>4a</sup>)R<sup>5</sup> where R<sup>4a</sup> is H or a prodrug ester, R<sup>5</sup> is alkyl or aryl or a phosphonic acid of the structure P(O)(OR<sup>4a</sup>)<sub>2</sub> where R<sup>4a</sup> is H or a prodrug ester;

or stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof. --

--37. (Amended) A pharmaceutical combination comprising a compound which has the

structure



wherein x is 1, 2, 3 or 4; m is 1 or 2; n is 1 or 2;

Q is C or N;

A is O or S;

Z is O or a bond;

R<sup>1</sup> is H or lower alkyl;

X is CH;

R<sup>2</sup> is H, alkyl, alkoxy, halogen, amino or substituted amino;

R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> are the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

R<sup>3</sup> is aryloxy carbonyl, alkyl oxy carbonyl, alkynyl oxy carbonyl, alkenyl oxy carbonyl,

alkyl(halo)aryloxy carbonyl, alkyl oxy(halo)aryloxy carbonyl cycloalkyl aryloxy carbonyl,

cycloalkyl oxy aryloxy carbonyl, alkyl carbonyl amino, aryl carbonyl amino, hetero aryl carbonyl amino,

alkoxy carbonyl amino, aryloxy carbonyl amino, hetero aryloxy carbonyl amino, alkyl sulfonyl,

alkenyl sulfonyl, hetero aryloxy carbonyl, cyclo hetero alkyl oxy carbonyl, hetero aryl alkenyl,

hydroxy alkyl, alkoxy, alkoxy aryloxy carbonyl, aryl alkyl oxy carbonyl, alkyl aryloxy carbonyl,

alkynyl oxy carbonyl, halo alkoxy aryloxy carbonyl, alkoxy carbonyl aryloxy carbonyl,

aryloxy aryloxy carbonyl, aryl alkenyl oxy carbonyl, hetero aryloxy aryl alkyl, aryloxy aryl alkyl oxy carbonyl,

aryloxy alkyl oxy carbonyl, aryl alkyl sulfonyl, aryl thiocarbonyl, aryl alkenyl sulfonyl, hetero aryl sulfonyl,

aryl sulfonyl, hetero aryl alkoxy carbonyl, hetero aryl alkyl oxy aryl alkyl, aryl alkenyl aryl alkyl,

aryl alkoxy carbonyl hetero aryl alkyl, hetero aryloxy aryl alkyl, aryl alkenyl hetero aryl alkyl or

poly halo alkyl aryloxy carbonyl;

Y is CO<sub>2</sub>R<sup>4</sup> where R<sup>4</sup> is H or alkyl, or a prodrug ester or Y is a C-linked 1-tetrazole, a

phosphinic acid of the structure P(O)(OR<sup>4a</sup>)R<sup>5</sup> here R<sup>4a</sup> is H or a prodrug ester, R<sup>5</sup> is alkyl or aryl or

a phosphonic acid of the structure P(O)(OR<sup>4a</sup>)<sub>2</sub> where R<sup>4a</sup> is H or a prodrug ester;

or stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts

thereof [as defined in Claim 1] and a lipid-lowering agent, a lipid modulating agent, an antidiabetic

agent, an anti-obesity agent, an antihypertensive agent, a platelet aggregation inhibitor, and/or an

antiosteoporosis agent. --

--39. (Amended) The combination as defined in Claim [38] 37 wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPAR $\alpha$  agonist, a PPAR  $\gamma$  agonist, a PPAR  $\alpha/\gamma$  dual agonist, an SGLT2 inhibitor, a DP4 inhibitor, an aP2 inhibitor, an insulin sensitizer, a glucagon-like peptide-I (GLP-I), insulin and/or a meglitinide; the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor agonist, an aP2 inhibitor and/or an anorectic agent; the lipid lowering agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, or an ACAT

inhibitor; the antihypertensive agent is an ACE inhibitor, angiotensin II receptor antagonist, NEP/ACE inhibitor, calcium channel blocker and/or  $\beta$ -adrenergic blocker. --

--40. (Amended) The combination as defined in Claim 39 wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipryride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, GI-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 and/or NVP-DPP-728A; the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol; the lipid lowering agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, itavastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, cholestagel, niacin and/or LY295427; the antihypertensive agent is an ACE inhibitor which is captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril or moexipril; an NEP/ACE inhibitor which is omapatrilat, [S[(R\*,R\*)]-hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (gemopatrilat) or CGS 30440;

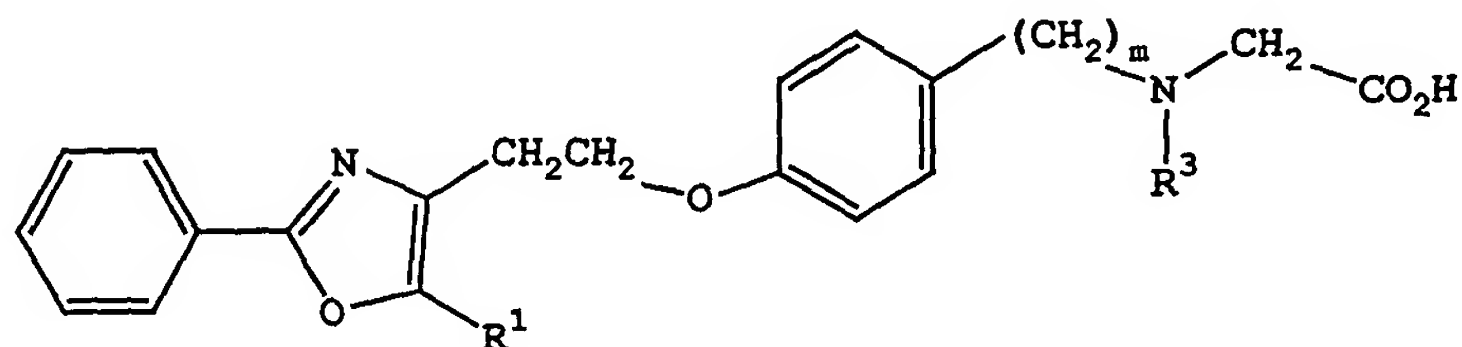
an angiotensin II receptor antagonist which is irbesartan, losartan or valsartan;

amlodipine besylate, prazosin HCl, verapamil, nifedipine, nadolol, propranolol, carvedilol, or clonidine HCl; the platelet aggregation inhibitor is aspirin, clopidogrel, ticlopidine, dipyridamole or ifetroban. --

--50. (Amended) A method for treating insulin resistance, hyperglycemia, hyperinsulinemia, or elevated blood levels of free fatty acids or glycerol, hyperlipidemia, obesity, Syndrome X, dysmetabolic syndrome, inflammation, diabetic complications, impaired glucose homeostasis, impaired glucose tolerance, hypertriglyceridemia, [or] atherosclerosis, or for treating irritable bowel syndrome, Crohn's disease, gastric ulceritis or osteoporosis, or psoriasis, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a pharmaceutical combination as defined in Claim [43] 37. --

New Claims 55 and 56 have been added as set out below.

55. A method for lowering blood glucose levels or for treating diabetes, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound which has the structure



where R¹ is alkyl,

(CH₂)<sub>m</sub> is CH₂ or  $\begin{array}{c} \text{CH}_3 \\ | \\ \text{---CH---} \end{array}$  and R³ is aryloxycarbonyl or alkoxyaryloxycarbonyl.

56. The method as defined in Claim 55 where in the compound employed (CH₂)<sub>m</sub> is CH₂.